Clinical trial results:
A Phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816 administered orally in adult patients with EGFRmut solid malignancies.

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

Summary

EudraCT number	2013-004482-14
Trial protocol	DE ES FR NL IT
Global end of trial date	15 August 2023

Results information

Result version number	v1 (current)
This version publication date	31 August 2024
First version publication date	31 August 2024

Trial information

Trial identification

Sponsor protocol code	CEGF816X2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02108964
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basl, 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	15 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I
• To estimate the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of EGF816.
Phase II
• To investigate the antitumor activity of EGF816 as measured by overall response rate (ORR) determined by Blinded Independent Review Committee (BIRC) assessment in accordance with RECIST 1.1.

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	06 June 2014
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	Canada: 24
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Singapore: 48
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	United States: 41

Worldwide total number of subjects	225
EEA total number of subjects	33

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)	133
From 65 to 84 years	92
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a 2-part study conducted in 14 investigative sites in 9 countries: Phase I part (dose-escalation) and Phase II part (dose expansion)

Pre-assignment

Screening details:

370 subjects were screened for eligibility during the 28 days prior to starting study treatment on Cycle 1 Day 1 (C1D1). The eligibility assessments were performed and ensured that all inclusion and exclusion criteria were satisfied

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	EGF816 75 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 75 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 75 mg administered orally on a continuous, once daily schedule.

Arm title	EGF816 100 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 100 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 100 mg administered orally on a continuous, once daily schedule.

Arm title	EGF816 150 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 150 mg orally once a day as continuous daily dosing in each cycle (of 28

days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 150 mg administered orally on a continuous, once daily schedule.

Arm title	EGF816 200 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 200 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 200 mg administered orally on a continuous, once daily schedule.
Note: 200 mg Tablet formulation was supplied to participants from Phase I and not provided to participants in Phase II (RP2D is 150 mg QD) participants.

Arm title	EGF816 225 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 225 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 225 mg administered orally on a continuous, once daily schedule.
Note: 200 mg Tablet formulation was supplied to participants from Phase I and not provided to participants in Phase II (RP2D is 150 mg QD) participants.

Arm title	EGF816 300 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 300 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental

Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 300 mg administered orally on a continuous, once daily schedule.
Note: 200 mg Tablet formulation was supplied to participants from Phase I and not provided to participants in Phase II (RP2D is 150 mg QD) participants.

Arm title	EGF816 350 mg (Phase I part)

Arm description:

Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 350 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase I-part first cohort of participants was 350 mg administered orally on a continuous, once daily schedule.
Note: 200 mg Tablet formulation was supplied to participants from Phase I and not provided to participants in Phase II (RP2D is 150 mg QD) participants.

Arm title	EGF816 150 mg (Phase II part)

Arm description:

Treatment naïve participants with locally advanced or metastatic NSCLC harboring EGFR mutations were administered with 150 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase II part of the study.

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	EGF816
Other name	Nazartinib
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

EGF816 was administered orally once per day with or without food on a continuous dosing schedule. The dose for this arm in this Phase II-part second cohort of participants was the recommended phase 2 dose (RP2D) of 150 mg administered orally on a continuous, once daily schedule.
Note: 200 mg Tablet formulation was supplied to participants from Phase I and not provided to participants in Phase II (RP2D is 150 mg QD) participants.

Number of subjects in period 1	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)
Started	17	38	73
Completed	0	0	0
Not completed	17	38	73
Adverse event, serious fatal	1	1	4

Physician decision	1	5	7
Study terminated by Sponsor	-	-	-
Adverse event, non-fatal	-	-	4
Subject/Guardian decision	-	1	4
Progressive disease	15	31	54

Number of subjects in period 1	EGF816 200 mg (Phase I part)	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)
Started	8	28	5
Completed	0	0	0
Not completed	8	28	5
Adverse event, serious fatal	-	3	-
Physician decision	1	2	1
Study terminated by Sponsor	-	-	-
Adverse event, non-fatal	-	1	-
Subject/Guardian decision	-	2	-
Progressive disease	7	20	4

Number of subjects in period 1	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Started	11	45
Completed	0	0
Not completed	11	45
Adverse event, serious fatal	-	2
Physician decision	1	3
Study terminated by Sponsor	-	3
Adverse event, non-fatal	3	2
Subject/Guardian decision	1	2
Progressive disease	6	33

Baseline characteristics

Reporting groups	
Reporting group title	EGF816 75 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 75 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 100 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 100 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 150 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 150 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 200 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 200 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 225 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 225 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 300 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 300 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 350 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 350 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 150 mg (Phase II part)
Reporting group description:	
Treatment naïve participants with locally advanced or metastatic NSCLC harboring EGFR mutations were administered with 150 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase II part of the study.	

Reporting group values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)
Number of subjects	17	38	73
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	10	23	47
>=65 years	7	15	26

Sex: Female, Male Units: Participants			
Female	13	23	50
Male	4	15	23
Race/Ethnicity, Customized Units: Subjects			
Asian	13	22	44
Caucasian	2	14	24
Unknown	2	2	3
Black	0	0	2

Reporting group values	EGF816 200 mg (Phase I part)	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)
Number of subjects	8	28	5
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	6	15	2
>=65 years	2	13	3
Sex: Female, Male Units: Participants			
Female	7	13	3
Male	1	15	2
Race/Ethnicity, Customized Units: Subjects			
Asian	6	21	4
Caucasian	2	7	1
Unknown	0	0	0
Black	0	0	0

Reporting group values	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)	Total
Number of subjects	11	45	225
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	7	23	133
>=65 years	4	22	92
Sex: Female, Male Units: Participants			
Female	7	27	143
Male	4	18	82
Race/Ethnicity, Customized Units: Subjects			
Asian	9	28	147
Caucasian	2	17	69
Unknown	0	0	7
Black	0	0	2

End points

End points reporting groups

Reporting group title	EGF816 75 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 75 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 100 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 100 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 150 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 150 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 200 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 200 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 225 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 225 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 300 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 300 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 350 mg (Phase I part)
Reporting group description:	
Participants with locally advanced or metastatic NSCLC harboring specific EGFR mutations were administered with EGF816 350 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase I part of the study.	
Reporting group title	EGF816 150 mg (Phase II part)
Reporting group description:	
Treatment naïve participants with locally advanced or metastatic NSCLC harboring EGFR mutations were administered with 150 mg orally once a day as continuous daily dosing in each cycle (of 28 days) during Phase II part of the study.	

Primary: Overall Response Rate (ORR) by Blinded Independent Review Committee (BIRC) (Phase II Part)

End point title	Overall Response Rate (ORR) by Blinded Independent Review Committee (BIRC) (Phase II Part)[1][2]
End point description:	
ORR is defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR) determined by BIRC assessment in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).	
End point type	Primary

End point timeframe:

From baseline up to 64 weeks

Notes:

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

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of participants				
number (confidence interval 95%)	64.4 (48.80 to 78.10)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Dose Limiting Toxicities (DLTs) (Phase I Part)

End point title	Number of participants with Dose Limiting Toxicities (DLTs) (Phase I Part)[3][4]

End point description:

Number of participants with DLTs during the first 28 days of therapy. A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle of treatment with EGF816 and meets any of the criteria described in the protocol. A participant with multiple occurrences of DLTs under one treatment is counted only once.

End point type	Primary

End point timeframe:

First 28 days of dosing

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistics analysis was done for this endpoint

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	38	69	7
Units: Participants	0	0	2	0

End point values	EGF816 225	EGF816 300	EGF816 350	

	mg (Phase I part)	mg (Phase I part)	mg (Phase I part)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	2	9	
Units: Participants	1	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) by Investigator assessment (Phase I & Phase II Parts)

End point title	Progression-free survival (PFS) by Investigator assessment (Phase I & Phase II Parts)

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression or death due to any cause determined by Investigator assessment in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	34	68	8
Units: Months				
median (confidence interval 95%)	6.3 (1.54 to 47.80)	12.1 (7.16 to 16.56)	7.4 (5.32 to 9.59)	13.7 (3.52 to 27.47)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	5	11	45
Units: Months				
median (confidence interval 95%)	11.1 (7.23 to 23.49)	11.8 (5.62 to 999)	11.0 (0.43 to 999)	18.2 (11.04 to 30.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by Investigator assessment (Phase I & II Parts)

End point title	Duration of Response (DOR) by Investigator assessment (Phase I & II Parts)

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause determined by Investigator assessment in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	17	34	5
Units: Months				
median (confidence interval 95%)	46.2 (3.68 to 99)	11.3 (7.39 to 23.79)	7.9 (7.39 to 11.04)	14.9 (9.20 to 999)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	3	4	29
Units: Months				
median (confidence interval 95%)	16.5 (5.52 to 29.63)	10.2 (9.33 to 999)	17.5 (7.56 to 999)	20.3 (11.01 to 34.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration (Cmax) of EGF816 and metabolite LMI258 (Phase I & Phase II part)

End point title	Observed maximum plasma concentration (Cmax) of EGF816 and metabolite LMI258 (Phase I & Phase II part)

End point description:

To characterize the PK properties of EGF816 and metabolite LMI258, Cmax will be calculated (Phase I & II parts).
Cmax is maximum (peak) observed plasma drug concentration (mass x volume-1).

End point type	Secondary

End point timeframe:

Cycle (C) 1 Day (D) 1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hours (hrs) post-dose), C1D15 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose) (for Phase I part only) and C2D1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose).

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	38	72	8
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1(n = 17, 36, 69, 8, 28, 5, 11, 45)	333 (± 64.9)	301 (± 81.8)	541 (± 53.2)	641 (± 60.2)
EFG816: C1D15 (n = 14, 36, 63, 7, 21, 1, 6, 0)	402 (± 62.3)	477 (± 53.0)	765 (± 50.1)	939 (± 45.4)
EFG816: C2D1 (n = 12, 24, 59, 7, 20, 3, 9, 26)	348 (± 43.4)	426 (± 50.1)	767 (± 46.7)	938 (± 53.9)
LMI258: C1D1 (n= 17, 36, 68, 8, 28, 5, 11, 38)	14.1 (± 174.8)	11.4 (± 76.1)	25.2 (± 61.7)	30.9 (± 64.6)
LMI258: C1D15 (n = 13, 34, 61, 7, 20, 1, 5, 0)	31.2 (± 94.7)	34.1 (± 81.8)	72.2 (± 64.0)	113 (± 54.1)
LMI258: C2D1 (n = 10, 30, 54, 6, 16, 3, 7, 13)	23.9 (± 59.5)	32.4 (± 76.0)	81.4 (± 55.4)	114 (± 75.1)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	5	11	45
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1(n = 17, 36, 69, 8, 28, 5, 11, 45)	935 (± 66.1)	1070 (± 58.3)	1190 (± 50.0)	471 (± 41.2)
EFG816: C1D15 (n = 14, 36, 63, 7, 21, 1, 6, 0)	1320 (± 46.0)	2670 (± 999)	1530 (± 23.5)	999 (± 999)
EFG816: C2D1 (n = 12, 24, 59, 7, 20, 3, 9, 26)	1270 (± 61.0)	1700 (± 41.3)	1270 (± 30.4)	648 (± 50.9)
LMI258: C1D1 (n= 17, 36, 68, 8, 28, 5, 11, 38)	42.0 (± 63.1)	62.2 (± 40.5)	52.7 (± 42.1)	24.3 (± 46.6)
LMI258: C1D15 (n = 13, 34, 61, 7, 20, 1, 5, 0)	131 (± 56.8)	292 (± 999)	164 (± 22.7)	999 (± 999)
LMI258: C2D1 (n = 10, 30, 54, 6, 16, 3, 7, 13)	101 (± 72.8)	142 (± 55.1)	116 (± 68.7)	62.5 (± 60.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma concentration (Tmax) of EGF816 and metabolite LMI258 (Phase I & Phase II part). Tmax is the time to reach maximum (peak) plasma drug concentration (time).

End point title	Time to Maximum Plasma concentration (Tmax) of EGF816 and metabolite LMI258 (Phase I & Phase II part). Tmax is the time to reach maximum (peak) plasma drug concentration (time).

End point description:

To characterize the PK properties of EGF816 and metabolite LMI258, Tmax will be calculated (Phase I & II parts). Tmax is the time to reach maximum (peak) plasma drug concentration (time).

End point type	Secondary

End point timeframe:

Cycle (C) 1 Day (D) 1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hours (hrs) post-dose), C1D15 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose) (for Phase I part only) and C2D1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose).

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	38	69	8
Units: hour (hr)				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1 (n =17,36,69,8,28,5,11,43)	2.83 (± 63.0)	3.24 (± 42.7)	2.74 (± 54.7)	3.66 (± 74.1)
EFG816: C1D15 (n = 14, 36, 63, 7, 21, 1, 6, 0)	2.91 (± 57.7)	2.75 (± 75.8)	3.11 (± 46.4)	3.52 (± 44.3)
EFG816: C2D1 (n = 12, 34, 59, 7, 20, 3, 9, 26)	3.13 (± 44.7)	2.81 (± 49.0)	3.14 (± 54.0)	3.53 (± 35.3)
LMI258: C1D1 (n= 17, 36, 68, 8, 28, 5, 11, 38)	2.54 (± 65.7)	3.14 (± 43.6)	2.78 (± 65.2)	3.19 (± 73.6)
LMI258: C1D15 (n = 13, 34, 61, 7, 20, 1, 5, 0)	2.89 (± 55.1)	2.76 (± 63.8)	3.32 (± 54.7)	4.05 (± 32.6)
LMI258: C2D1 (n = 10, 33, 57, 7, 19, 3, 8, 13)	3.38 (± 64.7)	3.04 (± 57.6)	3.43 (± 55.0)	5.00 (± 56.1)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	5	11	43
Units: hour (hr)				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1 (n =17,36,69,8,28,5,11,43)	2.64 (± 64.9)	3.37 (± 41.0)	3.45 (± 22.4)	2.81 (± 43.4)
EFG816: C1D15 (n = 14, 36, 63, 7, 21, 1, 6, 0)	3.46 (± 36.1)	6.08 (± 999)	4.45 (± 35.4)	999 (± 999)
EFG816: C2D1 (n = 12, 34, 59, 7, 20, 3, 9, 26)	3.17 (± 38.2)	2.99 (± 0.6)	3.97 (± 44.1)	3.48 (± 52.7)
LMI258: C1D1 (n= 17, 36, 68, 8, 28, 5, 11, 38)	2.99 (± 71.4)	3.37 (± 41.5)	3.53 (± 31.8)	2.70 (± 43.3)
LMI258: C1D15 (n = 13, 34, 61, 7, 20, 1, 5, 0)	4.03 (± 38.7)	7.12 (± 999)	4.54 (± 39.3)	999 (± 999)
LMI258: C2D1 (n = 10, 33, 57, 7, 19, 3, 8, 13)	3.26 (± 46.6)	3.77 (± 42.4)	4.13 (± 47.8)	3.92 (± 45.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau (AUCtau) of EGF816 and metabolite LMI258 (Phase I & Phase II part)

End point title	Area Under the Serum Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau (AUCtau) of EGF816 and metabolite LMI258 (Phase I & Phase II part)

End point description:

To characterize the PK properties of EGF816 and metabolite LMI258, AUCtau will be calculated (Phase I & II parts). AUCtau is the AUC calculated to the end of a dosing interval (tau) (amount x time x volume-1).

End point type	Secondary

End point timeframe:

Cycle (C) 1 Day (D) 1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hours (hrs) post-dose), C1D15 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose) (for Phase I part only) and C2D1 (pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hrs post-dose).

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	38	72	8
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1 (n = 16, 35, 66, 8, 26, 5, 11, 41)	4340 (± 68.2)	4000 (± 83.1)	6880 (± 53.3)	8310 (± 51.2)
EFG816: C1D15 (n = 13, 31, 57, 7, 18, 1, 5, 0)	6370 (± 61.1)	6770 (± 66.0)	11300 (± 53.2)	13500 (± 44.1)
EFG816: C2D1 (n = 12, 30, 56, 6, 17, 3, 7, 25)	5670 (± 44.7)	6150 (± 58.6)	11800 (± 50.3)	15800 (± 10.6)
LMI258: C1D1 (n= 15, 33, 65, 8, 26, 5, 11, 37)	182 (± 56.8)	162 (± 78.0)	330 (± 62.1)	424 (± 56.0)
LMI258: C1D15 (n = 13, 31, 57, 7, 19, 1, 5, 0)	466 (± 82.1)	523 (± 111.1)	1170 (± 69.5)	1810 (± 58.6)
LMI258: C2D1 (n = 10, 30, 54, 6, 16, 3, 7, 13)	402 (± 65.7)	499 (± 97.7)	1380 (± 58.6)	2340 (± 45.2)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	5	11	45
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
EFG816: C1D1 (n = 16, 35, 66, 8, 26, 5, 11, 41)	12100 (± 64.7)	15000 (± 61.0)	16900 (± 51.0)	5720 (± 42.7)
EFG816: C1D15 (n = 13, 31, 57, 7, 18, 1, 5, 0)	20300 (± 54.6)	51200 (± 999)	25700 (± 26.1)	999 (± 999)
EFG816: C2D1 (n = 12, 30, 56, 6, 17, 3, 7, 25)	18600 (± 66.5)	26100 (± 53.0)	22300 (± 19.0)	9830 (± 51.3)
LMI258: C1D1 (n= 15, 33, 65, 8, 26, 5, 11, 37)	559 (± 62.4)	859 (± 50.0)	810 (± 47.0)	291 (± 45.3)
LMI258: C1D15 (n = 13, 31, 57, 7, 19, 1, 5, 0)	2460 (± 65.2)	5940 (± 999)	3420 (± 45.6)	999 (± 999)
LMI258: C2D1 (n = 10, 30, 54, 6, 16, 3, 7, 13)	1760 (± 90.3)	2360 (± 65.9)	2820 (± 34.8)	1060 (± 67.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in H-score for immunohistochemistry (IHC) biomarkers from tumor tissue samples (Phase I part)

End point title	Percentage change from baseline in H-score for immunohistochemistry (IHC) biomarkers from tumor tissue samples (Phase I part)[5]

End point description:

Changes in EGFR signaling pathway of newly obtained tumor samples following EGF816 treatment were evaluated by IHC of three pharmacodynamics (PD) biomarkers: p-EGFR, p-AKT and p-ERK. The assigned H-score semi-quantitatively assessed the expression level of these protein markers and their phosphorylated forms.

End point type	Secondary

End point timeframe:

Baseline and Cycle 1 Day 15

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	38	73	8
Units: percentage change				
arithmetic mean (standard deviation)				
PD: P_AKT: Change from BL (n=1,5,10,4,9,2,4,0)	-10.0 (± 999)	-39.0 (± 78.2)	-31.8 (± 47.7)	3.5 (± 14.5)
PD: p-EGFR: Change from BL (n=1,5,10,4,9,2,4,0)	-165.0 (± 999)	-21.8 (± 43.9)	-19.5 (± 34.7)	-38.8 (± 50.1)
PD: p-ERK: Change from BL (n=1,5,10,4,8,2,4,0)	-60.0 (± 999)	-113.4 (± 84.2)	-2.4 (± 128.3)	33.5 (± 86.7)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	5	11	
Units: percentage change				
arithmetic mean (standard deviation)				
PD: P_AKT: Change from BL (n=1,5,10,4,9,2,4,0)	16.1 (± 65.3)	-2.5 (± 3.5)	-51.3 (± 71.9)	
PD: p-EGFR: Change from BL (n=1,5,10,4,9,2,4,0)	2.2 (± 23.7)	-32.5 (± 38.9)	-12.5 (± 18.9)	
PD: p-ERK: Change from BL (n=1,5,10,4,8,2,4,0)	8.8 (± 68.0)	-65.0 (± 35.4)	-1.3 (± 46.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by Investigator assessment (Phase I & II Parts)

End point title	Overall Response Rate (ORR) by Investigator assessment (Phase I & II Parts)

End point description:

ORR is defined as percentage of patients with best overall response of partial response (PR)+ complete response (CR) determined by Investigator assessment in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 4 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	34	68	8
Units: Percentage of participants				
number (not applicable)	41.7	50.0	50.0	62.5

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	5	11	45
Units: Percentage of participants				
number (not applicable)	62.5	60.0	36.4	55.6

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by Investigator assessment (Phase I & II Parts)

End point title	Disease Control Rate (DCR) by Investigator assessment (Phase I & II Parts)

End point description:

DCR is defined as the proportion of patients with best overall response of CR, PR, or SD determined by Investigator assessment in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 4 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	34	68	8
Units: Percentage of participants				
number (not applicable)	83.3	97.1	83.3	100.0

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	5	11	45
Units: Percentage of participants				
number (not applicable)	95.8	100.0	72.7	91.1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) by Investigator assessment (Phase I & II Parts)

End point title	Time to Response (TTR) by Investigator assessment (Phase I & II Parts)

End point description:

TTR is defined as the time from the date of the first dose to the date of first documented response (CR or PR) determined by Investigator assessment in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	34	68	8
Units: Months				
median (confidence interval 95%)	999 (1.64 to 999)	5.5 (1.81 to 999)	11.6 (1.87 to 999)	4.5 (1.64 to 999)

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	5	11	45
Units: Months				
median (confidence interval 95%)	1.9 (1.68 to 999)	1.7 (1.61 to 999)	999 (1.64 to 999)	1.9 (1.84 to 7.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with dose interruptions and dose reductions (Phase I & II Parts)

End point title	Number of participants with dose interruptions and dose reductions (Phase I & II Parts)

End point description:

Assessment of the tolerability of EGF816 will be performed continuously during the treatment phase

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

End point values	EGF816 75 mg (Phase I part)	EGF816 100 mg (Phase I part)	EGF816 150 mg (Phase I part)	EGF816 200 mg (Phase I part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	38	73	8
Units: Participants				
Participants with any dose Interruption	3	17	35	5
Participants with at least one dose reductions	0	1	9	1

End point values	EGF816 225 mg (Phase I part)	EGF816 300 mg (Phase I part)	EGF816 350 mg (Phase I part)	EGF816 150 mg (Phase II part)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	5	11	45
Units: Participants				
Participants with any dose Interruption	20	5	6	19
Participants with at least one dose reductions	17	4	6	9

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by BIRC (Phase II Part)

End point title	Disease Control Rate (DCR) by BIRC (Phase II Part)[6]

End point description:

DCR is defined as the percentage of patients with best overall response of CR, PR, or SD determined by BIRC in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of participants				
number (confidence interval 95%)	93.3 (81.70 to 98.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) by BIRC (Phase II Part)

End point title	Progression-Free Survival (PFS) by BIRC (Phase II Part)[7]

End point description:

PFS is defined as time from date of first dose of study treatment to date of first documented disease progression or death due to any cause determined by BIRC in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: months				
median (confidence interval 95%)	18.9 (14.75 to 29.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by BIRC (Phase II Part)

End point title	Duration of Response (DOR) by BIRC (Phase II Part)[8]

End point description:

DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause determined by BIRC in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
median (confidence interval 95%)	18.6 (14.88 to 31.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) by BIRC (Phase II Part)

End point title	Time to Response (TTR) by BIRC (Phase II Part)[9]

End point description:

TTR is defined as as the time from the date of first dose of study treatment to the date of first documented response (CR or PR) determined by by BIRC in accordance to RECIST 1.1

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Months				
median (confidence interval 95%)	48.3 (22.93 to 58.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) (Phase II Part)

End point title	Overall Survival (OS) (Phase II Part)[10]

End point description:

OS is defined as the time from first dose of the study treatment to the date of death due to any cause.

End point type	Secondary

End point timeframe:

At least 24 weeks up to approx. 9 years

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistics analysis was done for this endpoint

End point values	EGF816 150 mg (Phase II part)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Months				
median (confidence interval 95%)	48.3 (22.93 to 58.84)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) are collected from first dose of study treatment until end of study treatment plus 30 days post treatment. AEs reported in this record are from first dose of study treatment until 30 days after end of treatment, approx. 9 years.

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	75 mg
Reporting group description: 75 mg	
Reporting group title	100 mg
Reporting group description: 100 mg	
Reporting group title	150 mg
Reporting group description: 150 mg	
Reporting group title	200 mg
Reporting group description: 200 mg	
Reporting group title	All@subjects
Reporting group description: All@subjects	
Reporting group title	300 mg
Reporting group description: 300 mg	
Reporting group title	350 mg
Reporting group description: 350 mg	
Reporting group title	RP2D (150 mg - 1L)
Reporting group description: RP2D (150 mg - 1L)	
Reporting group title	225 mg
Reporting group description: 225 mg	

Serious adverse events	75 mg	100 mg	150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)	11 / 38 (28.95%)	40 / 73 (54.79%)
number of deaths (all causes)	3	1	13
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular lymphoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (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
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (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
Choking			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	4 / 73 (5.48%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatitis B DNA assay positive			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fever			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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
Hepatic failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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

Bacteraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	0 / 73 (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
Perihepatic abscess			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 17 (5.88%)	4 / 38 (10.53%)	6 / 73 (8.22%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia bacterial			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Septic shock			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected COVID-19			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	200 mg	All@subjects	300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	107 / 225 (47.56%)	4 / 5 (80.00%)
number of deaths (all causes)	0	31	0
number of deaths resulting from adverse events	0	1	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Follicular lymphoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Lymphoedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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			
Face oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Choking			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	7 / 225 (3.11%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (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
Major depression			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatitis B DNA assay positive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Fracture			

subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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 compression fracture			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fever			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Subdural haematoma			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Atrial tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Pericardial effusion			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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			
Ataxia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Altered state of consciousness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (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
Headache			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Hydrocephalus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Enteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Enterocolitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Haemorrhagic ascites			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Pancreatitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Cholestasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Hepatic failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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

Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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

COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Empyema			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Hepatitis B reactivation			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Meningitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Perihepatic abscess			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	21 / 225 (9.33%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 24	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (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
Pneumonia influenzal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected COVID-19			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (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
Hypervolaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (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

Serious adverse events	350 mg	RP2D (150 mg - 1L)	225 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	22 / 45 (48.89%)	16 / 28 (57.14%)
number of deaths (all causes)	1	6	7
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			

subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular lymphoma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (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
Cancer pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Face oedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (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
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choking			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatitis B DNA assay positive			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fever			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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
Hydrocephalus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (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
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (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
Enterocolitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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
Cholestasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (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

Nephrolithiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (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
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Lower respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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
Meningitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perihepatic abscess			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 11 (27.27%)	2 / 45 (4.44%)	4 / 28 (14.29%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (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	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected COVID-19			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (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
Decreased appetite			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	75 mg	100 mg	150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	36 / 38 (94.74%)	73 / 73 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2

Vascular disorders			
Flushing			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	2 / 17 (11.76%)	4 / 38 (10.53%)	2 / 73 (2.74%)
occurrences (all)	2	4	4
Hot flush			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	5 / 73 (6.85%)
occurrences (all)	1	1	5
Chest discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	2	0	4
Chills			
subjects affected / exposed	0 / 17 (0.00%)	4 / 38 (10.53%)	2 / 73 (2.74%)
occurrences (all)	0	4	2
Early satiety			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	8 / 17 (47.06%)	8 / 38 (21.05%)	21 / 73 (28.77%)
occurrences (all)	9	8	21
Oedema peripheral			
subjects affected / exposed	1 / 17 (5.88%)	5 / 38 (13.16%)	11 / 73 (15.07%)
occurrences (all)	1	8	16
Non-cardiac chest pain			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	10 / 73 (13.70%)
occurrences (all)	1	2	11
Influenza like illness			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	3 / 73 (4.11%)
occurrences (all)	0	6	9
Gait disturbance			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Xerosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	3
Swelling face			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	8 / 73 (10.96%)
occurrences (all)	0	4	10
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	5 / 17 (29.41%)	7 / 38 (18.42%)	21 / 73 (28.77%)
occurrences (all)	7	7	27
Dyspnoea exertional			

subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	6 / 17 (35.29%)	1 / 38 (2.63%)	13 / 73 (17.81%)
occurrences (all)	7	1	13
Dysphonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Dry throat			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	6 / 73 (8.22%)
occurrences (all)	0	1	6
Haemoptysis			
subjects affected / exposed	3 / 17 (17.65%)	0 / 38 (0.00%)	5 / 73 (6.85%)
occurrences (all)	6	0	5
Hiccups			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	1	0	2
Laryngeal inflammation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Pharyngeal inflammation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	0	0	3
Nasal dryness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	3 / 73 (4.11%)
occurrences (all)	0	1	3
Nasal congestion			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	2 / 73 (2.74%)
occurrences (all)	1	2	2
Orthopnoea			

subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Pulmonary embolism			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	1	3	2
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	0	0	3
Rhinorrhoea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	8 / 73 (10.96%)
occurrences (all)	3	1	8
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	1 / 73 (1.37%)
occurrences (all)	0	2	1
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Insomnia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 38 (5.26%)	8 / 73 (10.96%)
occurrences (all)	3	2	9
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	1 / 73 (1.37%)
occurrences (all)	0	4	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)	2 / 38 (5.26%)	5 / 73 (6.85%)
occurrences (all)	2	2	5
Amylase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)	4 / 38 (10.53%)	4 / 73 (5.48%)
occurrences (all)	3	5	4
Platelet count decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	1	0	5
Neutrophil count decreased			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	1 / 73 (1.37%)
occurrences (all)	1	3	2
Lipase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	2	0	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	1 / 73 (1.37%)
occurrences (all)	0	4	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	5 / 73 (6.85%)
occurrences (all)	1	2	13
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	1 / 73 (1.37%)
occurrences (all)	0	5	1
Weight decreased			

subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	3 / 73 (4.11%)
occurrences (all)	1	2	4
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Face injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	0 / 73 (0.00%)
occurrences (all)	0	4	0
Ligament sprain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	4
Radius fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Vascular access site haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Subdural haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			

subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Left ventricular dysfunction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Amnesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Ataxia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Hypoaesthesia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	1	2	1
Hyperaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	1 / 17 (5.88%)	7 / 38 (18.42%)	13 / 73 (17.81%)
occurrences (all)	1	10	14
Dysgeusia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	5 / 17 (29.41%)	6 / 38 (15.79%)	9 / 73 (12.33%)
occurrences (all)	5	7	10
Dementia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0

Cognitive disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Cerebral haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Taste disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Seizure			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Petit mal epilepsy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Neuropathy peripheral			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)	5 / 38 (13.16%)	10 / 73 (13.70%)
occurrences (all)	1	7	12
Neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	4 / 73 (5.48%)
occurrences (all)	0	1	5
Immune thrombocytopenia			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences (all)	1	1	0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Eosinophilia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	2 / 73 (2.74%)
occurrences (all)	0	2	6
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye discharge			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	4 / 73 (5.48%)
occurrences (all)	0	1	4
Ocular hyperaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	5 / 73 (6.85%)
occurrences (all)	0	0	5
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 17 (17.65%)	2 / 38 (5.26%)	4 / 73 (5.48%)
occurrences (all)	3	3	4
Abdominal distension			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	3 / 73 (4.11%)
occurrences (all)	1	1	3
Abdominal discomfort			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Aphthous ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	0	1	4
Ascites			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1
Cheilitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	5 / 73 (6.85%)
occurrences (all)	0	1	5
Diarrhoea			
subjects affected / exposed	4 / 17 (23.53%)	13 / 38 (34.21%)	29 / 73 (39.73%)
occurrences (all)	7	21	50
Constipation			
subjects affected / exposed	2 / 17 (11.76%)	10 / 38 (26.32%)	17 / 73 (23.29%)
occurrences (all)	2	15	23
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	5 / 73 (6.85%)
occurrences (all)	4	0	6
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	4 / 73 (5.48%)
occurrences (all)	0	3	4

Gastritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	3
Flatulence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Enterocolitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Odynophagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 17 (23.53%)	8 / 38 (21.05%)	15 / 73 (20.55%)
occurrences (all)	5	8	21
Ileus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	6 / 17 (35.29%)	6 / 38 (15.79%)	10 / 73 (13.70%)
occurrences (all)	9	6	13
Stomatitis			
subjects affected / exposed	8 / 17 (47.06%)	9 / 38 (23.68%)	20 / 73 (27.40%)
occurrences (all)	10	23	45
Oral pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Cutaneous vasculitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Acne			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	0	0	3
Dermatitis acneiform			
subjects affected / exposed	3 / 17 (17.65%)	4 / 38 (10.53%)	8 / 73 (10.96%)
occurrences (all)	4	4	10
Dermatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	4
Dry skin			
subjects affected / exposed	3 / 17 (17.65%)	9 / 38 (23.68%)	15 / 73 (20.55%)
occurrences (all)	3	9	15
Onychomadesis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1
Nail ridging			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1

Night sweats			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	3 / 73 (4.11%)
occurrences (all)	0	3	4
Rash			
subjects affected / exposed	3 / 17 (17.65%)	4 / 38 (10.53%)	4 / 73 (5.48%)
occurrences (all)	4	4	6
Pruritus			
subjects affected / exposed	4 / 17 (23.53%)	11 / 38 (28.95%)	28 / 73 (38.36%)
occurrences (all)	7	18	31
Petechiae			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	0	1	2
Rash maculo-papular			
subjects affected / exposed	4 / 17 (23.53%)	9 / 38 (23.68%)	29 / 73 (39.73%)
occurrences (all)	5	16	39
Rash macular			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	5 / 73 (6.85%)
occurrences (all)	2	2	9
Skin exfoliation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Skin fissures			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	3 / 73 (4.11%)
occurrences (all)	0	0	4

Skin hyperpigmentation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Skin mass			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Toxic skin eruption			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	3 / 17 (17.65%)	1 / 38 (2.63%)	5 / 73 (6.85%)
occurrences (all)	3	1	6
Vasculitic rash			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Skin striae			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Hypertonic bladder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Nocturia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	2	1	1
Polyuria			

subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	1 / 73 (1.37%)
occurrences (all)	0	5	1
Muscle spasms			
subjects affected / exposed	1 / 17 (5.88%)	6 / 38 (15.79%)	11 / 73 (15.07%)
occurrences (all)	2	8	13
Flank pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	3 / 73 (4.11%)
occurrences (all)	1	1	3
Bone pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 17 (5.88%)	7 / 38 (18.42%)	5 / 73 (6.85%)
occurrences (all)	1	8	5
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)	6 / 38 (15.79%)	9 / 73 (12.33%)
occurrences (all)	1	6	10
Back pain			
subjects affected / exposed	4 / 17 (23.53%)	6 / 38 (15.79%)	11 / 73 (15.07%)
occurrences (all)	4	7	11
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)	6 / 38 (15.79%)	8 / 73 (10.96%)
occurrences (all)	1	6	9
Osteoporosis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	6 / 73 (8.22%)
occurrences (all)	0	0	6
Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	6 / 73 (8.22%)
occurrences (all)	4	3	6
Musculoskeletal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	0 / 73 (0.00%)
occurrences (all)	0	3	0
Genital herpes			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Dermatitis infected			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	2 / 73 (2.74%)
occurrences (all)	0	3	2
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)	1 / 38 (2.63%)	2 / 73 (2.74%)
occurrences (all)	1	1	2
Herpes zoster reactivation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0

Influenza			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)	4 / 38 (10.53%)	5 / 73 (6.85%)
occurrences (all)	5	5	6
Onychomycosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	1 / 17 (5.88%)	3 / 38 (7.89%)	12 / 73 (16.44%)
occurrences (all)	2	3	15
Tuberculosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	0 / 73 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	3 / 73 (4.11%)
occurrences (all)	0	1	3
Rash pustular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0

Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	4 / 73 (5.48%)
occurrences (all)	0	3	5
Pharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 38 (5.26%)	2 / 73 (2.74%)
occurrences (all)	1	2	2
Wound infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)	3 / 38 (7.89%)	4 / 73 (5.48%)
occurrences (all)	2	4	7
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	9 / 38 (23.68%)	7 / 73 (9.59%)
occurrences (all)	2	10	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 17 (29.41%)	4 / 38 (10.53%)	16 / 73 (21.92%)
occurrences (all)	7	5	17
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	3 / 38 (7.89%)	1 / 73 (1.37%)
occurrences (all)	0	3	1
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	2 / 73 (2.74%)
occurrences (all)	0	2	2
Hyperkalaemia			
subjects affected / exposed	1 / 17 (5.88%)	3 / 38 (7.89%)	4 / 73 (5.48%)
occurrences (all)	1	5	10
Hyperuricaemia			

subjects affected / exposed	0 / 17 (0.00%)	2 / 38 (5.26%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 38 (2.63%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	1 / 73 (1.37%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 38 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	200 mg	All@subjects	300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	220 / 225 (97.78%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	20 / 225 (8.89%)	0 / 5 (0.00%)
occurrences (all)	1	24	0
Hot flush			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	13 / 225 (5.78%)	1 / 5 (20.00%)
occurrences (all)	0	19	1
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	0	12	0
Chills			
subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Early satiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	3 / 8 (37.50%)	59 / 225 (26.22%)	3 / 5 (60.00%)
occurrences (all)	6	67	3
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	27 / 225 (12.00%)	2 / 5 (40.00%)
occurrences (all)	2	36	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	18 / 225 (8.00%)	0 / 5 (0.00%)
occurrences (all)	0	19	0
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	1	21	0
Gait disturbance			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Xerosis			

subjects affected / exposed	1 / 8 (12.50%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	1	6	0
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	34 / 225 (15.11%)	2 / 5 (40.00%)
occurrences (all)	1	46	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Seasonal allergy			
subjects affected / exposed	1 / 8 (12.50%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Pelvic pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	3 / 8 (37.50%)	64 / 225 (28.44%)	2 / 5 (40.00%)
occurrences (all)	3	81	2
Dyspnoea exertional			
subjects affected / exposed	1 / 8 (12.50%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	1	9	0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	36 / 225 (16.00%)	1 / 5 (20.00%)
occurrences (all)	0	40	1
Dysphonia			

subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Dry throat			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	11 / 225 (4.89%)	2 / 5 (40.00%)
occurrences (all)	0	11	2
Haemoptysis			
subjects affected / exposed	1 / 8 (12.50%)	16 / 225 (7.11%)	1 / 5 (20.00%)
occurrences (all)	1	20	1
Hiccups			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Laryngeal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Nasal dryness			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Orthopnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Pulmonary embolism			

subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	1 / 5 (20.00%)
occurrences (all)	0	12	1
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	1 / 5 (20.00%)
occurrences (all)	0	6	1
Rhinorrhoea			
subjects affected / exposed	2 / 8 (25.00%)	19 / 225 (8.44%)	0 / 5 (0.00%)
occurrences (all)	2	24	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	2	7	0
Depressed mood			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Insomnia			
subjects affected / exposed	3 / 8 (37.50%)	22 / 225 (9.78%)	0 / 5 (0.00%)
occurrences (all)	3	25	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	1 / 5 (20.00%)
occurrences (all)	0	7	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	1 / 5 (20.00%)
occurrences (all)	0	9	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	18 / 225 (8.00%)	0 / 5 (0.00%)
occurrences (all)	0	23	0
Amylase increased			

subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	0	14	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	17 / 225 (7.56%)	0 / 5 (0.00%)
occurrences (all)	0	20	0
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	12 / 225 (5.33%)	1 / 5 (20.00%)
occurrences (all)	0	18	4
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	0	8	0
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	11 / 225 (4.89%)	0 / 5 (0.00%)
occurrences (all)	0	17	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	1 / 5 (20.00%)
occurrences (all)	0	9	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	2 / 5 (40.00%)
occurrences (all)	0	7	4
Blood creatinine increased			
subjects affected / exposed	1 / 8 (12.50%)	16 / 225 (7.11%)	1 / 5 (20.00%)
occurrences (all)	1	28	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	0	13	0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	13 / 225 (5.78%)	0 / 5 (0.00%)
occurrences (all)	0	14	0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Face injury			

subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Ligament sprain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	10 / 225 (4.44%)	0 / 5 (0.00%)
occurrences (all)	0	10	0
Radius fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vascular access site haematoma			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Subdural haematoma			
subjects affected / exposed	1 / 8 (12.50%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Cardiac failure congestive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Angina pectoris			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Left ventricular dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1

Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Amnesia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Ataxia			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Hypoaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
Hyperaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	3 / 8 (37.50%)	41 / 225 (18.22%)	1 / 5 (20.00%)
occurrences (all)	5	54	1
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	7 / 225 (3.11%)	0 / 5 (0.00%)
occurrences (all)	0	12	0
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	32 / 225 (14.22%)	2 / 5 (40.00%)
occurrences (all)	1	34	2
Dementia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Cognitive disorder			
subjects affected / exposed	1 / 8 (12.50%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Cerebral haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tremor			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Taste disorder			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Seizure			
subjects affected / exposed	1 / 8 (12.50%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
Petit mal epilepsy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Neuropathy peripheral			
subjects affected / exposed	2 / 8 (25.00%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	2	6	0
Memory impairment			
subjects affected / exposed	1 / 8 (12.50%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	35 / 225 (15.56%)	3 / 5 (60.00%)
occurrences (all)	0	43	3
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	10 / 225 (4.44%)	0 / 5 (0.00%)
occurrences (all)	1	17	0
Immune thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eosinophilia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	7 / 225 (3.11%)	1 / 5 (20.00%)
occurrences (all)	1	12	2
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	1 / 5 (20.00%)
occurrences (all)	0	11	1
Ocular hyperaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	2 / 8 (25.00%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	2	9	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	16 / 225 (7.11%)	0 / 5 (0.00%)
occurrences (all)	0	17	0
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Abdominal discomfort			

subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	13 / 225 (5.78%)	1 / 5 (20.00%)
occurrences (all)	0	17	2
Aphthous ulcer			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	1 / 5 (20.00%)
occurrences (all)	0	6	1
Ascites			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Cheilitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	1 / 5 (20.00%)
occurrences (all)	0	9	1
Diarrhoea			
subjects affected / exposed	4 / 8 (50.00%)	102 / 225 (45.33%)	5 / 5 (100.00%)
occurrences (all)	10	179	8
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	42 / 225 (18.67%)	0 / 5 (0.00%)
occurrences (all)	1	59	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	15 / 225 (6.67%)	1 / 5 (20.00%)
occurrences (all)	0	21	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	11 / 225 (4.89%)	1 / 5 (20.00%)
occurrences (all)	0	12	1
Gastritis			
subjects affected / exposed	1 / 8 (12.50%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	1	10	0
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	1 / 5 (20.00%)
occurrences (all)	0	5	1
Enterocolitis			

subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Odynophagia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	54 / 225 (24.00%)	2 / 5 (40.00%)
occurrences (all)	3	73	5
Ileus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	38 / 225 (16.89%)	1 / 5 (20.00%)
occurrences (all)	0	48	3
Stomatitis			
subjects affected / exposed	3 / 8 (37.50%)	67 / 225 (29.78%)	1 / 5 (20.00%)
occurrences (all)	6	129	1
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Alopecia			

subjects affected / exposed	0 / 8 (0.00%)	9 / 225 (4.00%)	1 / 5 (20.00%)
occurrences (all)	0	9	1
Acne			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Dermatitis acneiform			
subjects affected / exposed	1 / 8 (12.50%)	34 / 225 (15.11%)	0 / 5 (0.00%)
occurrences (all)	1	40	0
Dermatitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Decubitus ulcer			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	6	0
Dry skin			
subjects affected / exposed	1 / 8 (12.50%)	52 / 225 (23.11%)	3 / 5 (60.00%)
occurrences (all)	1	52	3
Onychomadesis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Eczema asteatotic			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Nail ridging			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	2 / 8 (25.00%)	10 / 225 (4.44%)	0 / 5 (0.00%)
occurrences (all)	3	12	0
Rash			

subjects affected / exposed	0 / 8 (0.00%)	24 / 225 (10.67%)	1 / 5 (20.00%)
occurrences (all)	0	31	1
Pruritus			
subjects affected / exposed	5 / 8 (62.50%)	82 / 225 (36.44%)	3 / 5 (60.00%)
occurrences (all)	5	110	5
Petechiae			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Rash erythematous			
subjects affected / exposed	2 / 8 (25.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	2	6	0
Skin discolouration			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Rash papular			
subjects affected / exposed	1 / 8 (12.50%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	1	9	0
Rash maculo-papular			
subjects affected / exposed	4 / 8 (50.00%)	89 / 225 (39.56%)	5 / 5 (100.00%)
occurrences (all)	6	124	7
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	15 / 225 (6.67%)	2 / 5 (40.00%)
occurrences (all)	0	21	2
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Skin fissures			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	1 / 5 (20.00%)
occurrences (all)	0	9	1
Skin hyperpigmentation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Skin mass			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Toxic skin eruption			

subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urticaria			
subjects affected / exposed	1 / 8 (12.50%)	19 / 225 (8.44%)	0 / 5 (0.00%)
occurrences (all)	1	22	0
Vasculitic rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Skin striae			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Hypertonic bladder			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urinary incontinence			
subjects affected / exposed	2 / 8 (25.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	2	4	0
Nocturia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Polyuria			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Micturition urgency			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0

Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	9 / 225 (4.00%)	0 / 5 (0.00%)
occurrences (all)	1	13	0
Muscle spasms			
subjects affected / exposed	3 / 8 (37.50%)	26 / 225 (11.56%)	1 / 5 (20.00%)
occurrences (all)	4	32	1
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	17 / 225 (7.56%)	0 / 5 (0.00%)
occurrences (all)	0	18	0
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	26 / 225 (11.56%)	0 / 5 (0.00%)
occurrences (all)	0	30	0
Back pain			
subjects affected / exposed	2 / 8 (25.00%)	34 / 225 (15.11%)	1 / 5 (20.00%)
occurrences (all)	2	35	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	20 / 225 (8.89%)	0 / 5 (0.00%)
occurrences (all)	0	21	0
Osteoporosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	0	8	0
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	16 / 225 (7.11%)	0 / 5 (0.00%)
occurrences (all)	1	20	0
Musculoskeletal discomfort			

subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Genital herpes			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis viral			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Dermatitis infected			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	10 / 225 (4.44%)	0 / 5 (0.00%)
occurrences (all)	1	10	0
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	10 / 225 (4.44%)	1 / 5 (20.00%)
occurrences (all)	0	10	1
Herpes zoster reactivation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	22 / 225 (9.78%)	0 / 5 (0.00%)
occurrences (all)	1	36	0

Onychomycosis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Paronychia			
subjects affected / exposed	2 / 8 (25.00%)	32 / 225 (14.22%)	1 / 5 (20.00%)
occurrences (all)	2	43	1
Tuberculosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Skin infection			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	3 / 225 (1.33%)	1 / 5 (20.00%)
occurrences (all)	1	3	1
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	7 / 225 (3.11%)	1 / 5 (20.00%)
occurrences (all)	0	7	1
Rash pustular			
subjects affected / exposed	0 / 8 (0.00%)	2 / 225 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	12 / 225 (5.33%)	1 / 5 (20.00%)
occurrences (all)	0	14	1
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	1	8	0
Wound infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Viral upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	4 / 225 (1.78%)	0 / 5 (0.00%)
occurrences (all)	2	5	0
Viral infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 225 (0.44%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	19 / 225 (8.44%)	0 / 5 (0.00%)
occurrences (all)	6	29	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 8 (37.50%)	36 / 225 (16.00%)	0 / 5 (0.00%)
occurrences (all)	5	48	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 8 (25.00%)	54 / 225 (24.00%)	2 / 5 (40.00%)
occurrences (all)	2	62	3
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	11 / 225 (4.89%)	0 / 5 (0.00%)
occurrences (all)	0	22	0
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	8 / 225 (3.56%)	0 / 5 (0.00%)
occurrences (all)	0	10	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 225 (2.22%)	1 / 5 (20.00%)
occurrences (all)	0	5	1
Hypokalaemia			

subjects affected / exposed	0 / 8 (0.00%)	10 / 225 (4.44%)	0 / 5 (0.00%)
occurrences (all)	0	14	0
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	7 / 225 (3.11%)	2 / 5 (40.00%)
occurrences (all)	1	11	2
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	6 / 225 (2.67%)	1 / 5 (20.00%)
occurrences (all)	0	7	2
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	6 / 225 (2.67%)	1 / 5 (20.00%)
occurrences (all)	1	10	1

Non-serious adverse events	350 mg	RP2D (150 mg - 1L)	225 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	42 / 45 (93.33%)	28 / 28 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	8 / 45 (17.78%)	2 / 28 (7.14%)
occurrences (all)	1	10	2
Hot flush			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 45 (6.67%)	1 / 28 (3.57%)
occurrences (all)	1	4	6
Chest discomfort			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	2 / 28 (7.14%)
occurrences (all)	0	4	2

Chills			
subjects affected / exposed	2 / 11 (18.18%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Early satiety			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	5 / 45 (11.11%)	8 / 28 (28.57%)
occurrences (all)	5	6	9
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	5 / 45 (11.11%)	1 / 28 (3.57%)
occurrences (all)	0	6	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	2 / 28 (7.14%)
occurrences (all)	0	3	2
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	1	4
Gait disturbance			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	2	1
Peripheral swelling			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Swelling face			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 11 (18.18%)	12 / 45 (26.67%)	6 / 28 (21.43%)
occurrences (all)	2	18	8
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	2 / 11 (18.18%)	14 / 45 (31.11%)	10 / 28 (35.71%)
occurrences (all)	3	20	12
Dyspnoea exertional			
subjects affected / exposed	1 / 11 (9.09%)	2 / 45 (4.44%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)	6 / 45 (13.33%)	8 / 28 (28.57%)
occurrences (all)	1	8	9
Dysphonia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	1	1	1
Dry throat			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Haemoptysis			

subjects affected / exposed	3 / 11 (27.27%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	3	2	2
Hiccups			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	3 / 28 (10.71%)
occurrences (all)	0	3	3
Nasal dryness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Orthopnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences (all)	0	2	3
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			

subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	6 / 28 (21.43%)
occurrences (all)	0	3	7
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Depressed mood			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	5 / 45 (11.11%)	2 / 28 (7.14%)
occurrences (all)	0	5	3
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	5 / 45 (11.11%)	3 / 28 (10.71%)
occurrences (all)	1	9	4
Amylase increased			
subjects affected / exposed	1 / 11 (9.09%)	6 / 45 (13.33%)	1 / 28 (3.57%)
occurrences (all)	1	10	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	2 / 28 (7.14%)
occurrences (all)	1	4	3
Platelet count decreased			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	4 / 28 (14.29%)
occurrences (all)	0	3	5
Neutrophil count decreased			

subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	0 / 11 (0.00%)	6 / 45 (13.33%)	1 / 28 (3.57%)
occurrences (all)	0	10	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	3	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	4 / 28 (14.29%)
occurrences (all)	1	4	5
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	4 / 28 (14.29%)
occurrences (all)	0	1	6
Weight decreased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 45 (2.22%)	4 / 28 (14.29%)
occurrences (all)	2	1	4
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Face injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Ligament sprain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Procedural pain			

subjects affected / exposed	1 / 11 (9.09%)	2 / 45 (4.44%)	3 / 28 (10.71%)
occurrences (all)	1	2	3
Radius fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vascular access site haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Subdural haematoma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Cardiac failure congestive			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Amnesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Ataxia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	9 / 45 (20.00%)	6 / 28 (21.43%)
occurrences (all)	1	14	8
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	0 / 28 (0.00%)
occurrences (all)	1	9	0
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	4 / 28 (14.29%)
occurrences (all)	1	4	4
Dementia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cerebral haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Seizure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Petit mal epilepsy			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Memory impairment			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 11 (36.36%)	5 / 45 (11.11%)	7 / 28 (25.00%)
occurrences (all)	4	8	8
Neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	9	1
Immune thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			

Ear haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences (all)	0	4	1
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	2 / 28 (7.14%)
occurrences (all)	1	4	2
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	2	2
Abdominal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	2 / 11 (18.18%)	5 / 45 (11.11%)	1 / 28 (3.57%)
occurrences (all)	4	6	1
Aphthous ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Ascites			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Dry mouth			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	9 / 11 (81.82%)	21 / 45 (46.67%)	17 / 28 (60.71%)
occurrences (all)	17	36	30
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	8 / 45 (17.78%)	4 / 28 (14.29%)
occurrences (all)	0	10	8
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	3 / 28 (10.71%)
occurrences (all)	1	6	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	1 / 28 (3.57%)
occurrences (all)	0	4	1
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Enterocolitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	1 / 11 (9.09%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Odynophagia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Nausea			

subjects affected / exposed	3 / 11 (27.27%)	10 / 45 (22.22%)	10 / 28 (35.71%)
occurrences (all)	4	14	13
Ileus			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	5 / 45 (11.11%)	8 / 28 (28.57%)
occurrences (all)	2	5	10
Stomatitis			
subjects affected / exposed	3 / 11 (27.27%)	12 / 45 (26.67%)	11 / 28 (39.29%)
occurrences (all)	4	16	24
Oral pain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	5 / 45 (11.11%)	1 / 28 (3.57%)
occurrences (all)	0	5	1
Acne			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	3 / 11 (27.27%)	10 / 45 (22.22%)	5 / 28 (17.86%)
occurrences (all)	3	12	6
Dermatitis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	5 / 11 (45.45%)	5 / 45 (11.11%)	11 / 28 (39.29%)
occurrences (all)	5	5	11
Onychomadesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nail ridging			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	2 / 11 (18.18%)	8 / 45 (17.78%)	2 / 28 (7.14%)
occurrences (all)	3	11	2
Pruritus			
subjects affected / exposed	6 / 11 (54.55%)	13 / 45 (28.89%)	12 / 28 (42.86%)
occurrences (all)	6	17	21
Petechiae			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			

subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Skin discolouration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Rash papular			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	3 / 28 (10.71%)
occurrences (all)	0	1	4
Rash maculo-papular			
subjects affected / exposed	6 / 11 (54.55%)	17 / 45 (37.78%)	15 / 28 (53.57%)
occurrences (all)	7	20	24
Rash macular			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	4 / 28 (14.29%)
occurrences (all)	0	2	4
Skin exfoliation			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Skin fissures			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	3 / 28 (10.71%)
occurrences (all)	0	1	3
Skin hyperpigmentation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin mass			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Toxic skin eruption			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	2 / 11 (18.18%)	3 / 45 (6.67%)	4 / 28 (14.29%)
occurrences (all)	2	3	6
Vasculitic rash			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin striae			

subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Hypertonic bladder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Polyuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	2	2	2
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
Flank pain			

subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	4 / 45 (8.89%)	0 / 28 (0.00%)
occurrences (all)	0	4	0
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	7 / 45 (15.56%)	3 / 28 (10.71%)
occurrences (all)	0	10	3
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	4 / 45 (8.89%)	5 / 28 (17.86%)
occurrences (all)	1	4	5
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	2 / 28 (7.14%)
occurrences (all)	0	3	2
Osteoporosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	2 / 11 (18.18%)	1 / 45 (2.22%)	3 / 28 (10.71%)
occurrences (all)	2	1	3
Musculoskeletal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0

Conjunctivitis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Dermatitis infected			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	2	1	1
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	4 / 45 (8.89%)	1 / 28 (3.57%)
occurrences (all)	0	4	1
Herpes zoster reactivation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	6 / 45 (13.33%)	4 / 28 (14.29%)
occurrences (all)	0	10	9
Onychomycosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	4 / 11 (36.36%)	5 / 45 (11.11%)	4 / 28 (14.29%)
occurrences (all)	8	5	7

Tuberculosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Rash pustular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 45 (4.44%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Wound infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	7 / 45 (15.56%)	1 / 28 (3.57%)
occurrences (all)	0	9	1

Upper respiratory tract infection			
subjects affected / exposed	2 / 11 (18.18%)	7 / 45 (15.56%)	7 / 28 (25.00%)
occurrences (all)	2	9	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 11 (45.45%)	13 / 45 (28.89%)	7 / 28 (25.00%)
occurrences (all)	6	15	7
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 45 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 45 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 45 (2.22%)	1 / 28 (3.57%)
occurrences (all)	1	4	1
Hyperuricaemia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 45 (6.67%)	2 / 28 (7.14%)
occurrences (all)	1	4	3
Hypoalbuminaemia			
subjects affected / exposed	0 / 11 (0.00%)	4 / 45 (8.89%)	1 / 28 (3.57%)
occurrences (all)	0	5	1
Hypocalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 45 (4.44%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	1 / 11 (9.09%)	5 / 45 (11.11%)	3 / 28 (10.71%)
occurrences (all)	1	7	5
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 45 (2.22%)	2 / 28 (7.14%)
occurrences (all)	0	1	6
Hypophosphataemia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 45 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	3	1
Hyponatraemia			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 45 (4.44%) 5	2 / 28 (7.14%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	Amendment 1: - Inclusion of a generic statement to comply with health authority's request to add a generic statement to this first-in-man trial: "that all participants participating in this clinical trial must have recurred or progressed following standard therapy, unless no standard therapy exists, is tolerated or appropriate". - Modifications to specific inclusion criteria that all participants participating in this clinical trial must have recurred or progressed following standard therapy, unless no standard therapy exists, is tolerated or appropriate; Phase I part to recruit NSCLC participants harboring a documented EGFR T790M mutation; The group 1 in Phase II part to recruit participants had advanced NSCLC with EGFR mutation (L858R or ex19del, not T790M) and were intolerant to an approved EGFR TKI (e.g., erlotinib, gefitinib, afatinib); and/or for whom these drugs were not appropriate.
04 June 2014	Amendment 2: The rational for the amendment was to address the changes requested by health authority (i.e. Japan PMDA) and included the following: Clarify the definition of "women of childbearing potential", Add "glucose" into chemistry panel in laboratory parameters, Clarify that results of biomarker will be returned to investigators.
21 August 2014	Amendment 3: The main purpose of this amendment was to allow for the possibility of a formulation change during dose escalation from capsule to tablet, and the determination of a MTD and/or RP2D with either formulation.
05 May 2015	Amendment 4: The primary purpose of this amendment was to revise the participant populations and/or the number of participants to be enrolled in each group in the Phase II part. In addition, the number of groups in the Phase II part was revised from four groups (as per Amendment 3) to six groups (Amendment 4). Each group had a distinctive participant population, determined by the specific EGFR mutations and the number of prior lines of systemic antineoplastic therapy, including prior EGFR TKIs. Throughout this amendment, advanced NSCLC referred to participants with either locally advanced or metastatic NSCLC. Locally advanced NSCLC was defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC referred to stage IV NSCLC.
31 August 2015	Amendment 5: As of 23-July-2015, 121 participants had been enrolled in the Phase I part (dose-escalation) of the study at nine sites in eight countries in Asia, Europe, and North America. As of 08-July-2015, two SAEs of HBV reactivation had been reported in two participants participating in the CEGF816X2101 study. One case had a fatal outcome due to hepatic failure despite initiation of antiviral treatment after HBV reactivation, and the second case was HBV reactivation that was medically significant. The viral reactivation in these two participants was likely due to immunosuppression related to nazartinib. To ensure the safety of all participants participating in EGF816X2101 trial, changes were made to the protocol to implement the safety regarding the reactivation of HBV and HCV. Early preclinical and clinical findings suggested that nazartinib might have an immunomodulatory effect, related to its ability to inhibit the Tec family of kinases. Changes were made to the protocol to allow sample acquisition at time points at which the presence of such an effect could be evaluated.

07 April 2017	Amendment 6: As of 31-Mar-2017 in the Phase I part (dose-escalation) of the study, 180 participants were enrolled with 7 different dose levels at 10 sites in 8 countries. During a dose escalation meeting on 30-Aug-2016, the Investigators and Novartis agreed to declare the RP2D of EGF816 capsules & tablets at the dose level of 150 mg qd based on the available safety, PK, efficacy data & on the BLRM recommendation. The Phase II part (expansion phase) was originally planned to enroll participants in 6 different groups defined by the prior lines of treatment & the tumor molecular status of the participants. However, the rapid evolving landscape including ongoing trials in this disease setting led to the decision not to start the enrollment of participants who received more than 1 line of prior antineoplastic therapy in Groups 2 to 6. Indeed, approval was granted in different countries to osimertinib for the treatment of adult participants with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after prior systemic therapy, including an EGFR-TKI giving participants in this setting access to 3rd generation EGFR-TKI as per FDA & EMA information. Therefore, the Phase II part of the study continued as a single group of participants, all treated at 150 mg qd EGF816. An Investigator letter dated 07-Dec-2016 informed the investigators about the opening of the Phase II part of the study for enrollment in Group 1 only. This group now enrolled a minimum of 40 treatment naïve participants instead of 60 participants who had locally advanced or metastatic NSCLC with EGFR activating mutation, had not received any systemic antineoplastic therapy for advanced NSCLC, & were eligible to receive EGFR-TKI treatment. The main purpose of this amendment was to implement the above-mentioned decisions that were already communicated to all Investigators & submitted to all Ethics Committees and Health Authorities in participating countries.
11 March 2020	Amendment 7: The main purpose of this amendment is to implement the use of the capsules form again (25 mg / 50 mg / 100 mg) instead of tablets for the ongoing participants promptly upon availability. The decision to switch back from tablet to capsule is based on the following: The capsule formulation has a superior stability profile compared to the tablets, allowing the assignment of longer shelf lives; Statistical analysis showed that exposures between tablet and capsule are comparable with geometric mean ratios of 1.04 and 1.03 for AUCtau and Cmax, respectively, following single 150 mg dose, and 1.06 and 1.12 for AUCtau and Cmax, respectively, following 150 mg QD. Therefore, based on this rationale, capsules were used in a timely manner following approval of this amendment for the remainder of this study for all ongoing participants in Phase I and Phase II parts. Additionally, the guidelines for some selected toxicities (hepatitis B, skin rash, including maculo-papular rash and Interstitial Lung Disease (ILD)/pneumonitis) had been updated to optimize the participant’s safety. These changes were not due to new safety findings but reflect new internal/international clinical guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: