Clinical trial results:
A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with FGFR Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with FGFR2 Gene Fusion

Summary

EudraCT number	2015-001443-36
Trial protocol	IT
Global end of trial date	28 August 2018

Results information

Result version number	v1
This version publication date	08 September 2021
First version publication date	08 September 2021

Trial information

Trial identification

Sponsor protocol code	ARQ 087-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01752920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd.
Sponsor organisation address	Grenzacherstrasse 487, Basel, Switzerland, 4005
Public contact	Head of Development, Basilea Pharmaceutica International Ltd., +41 61 606 12 25, stephan.braun@basilea.com
Scientific contact	Head of Development, Basilea Pharmaceutica International Ltd., +41 61 606 12 25, stephan.braun@basilea.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	03 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2018
Global end of trial reached?	Yes
Global end of trial date	28 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this first-in-humans study was to assess the safety and tolerability of ARQ 087 in patients with advanced solid tumors (Part 1; Dose Escalation/Food-effect Cohorts) or with advanced solid tumors with FGFR genetic aberrations, including iCCA with FGFR2 gene fusion (Part 2; Expanded Cohort, signal finding).

Protection of trial subjects:

No additional pain or distress was caused by the use of the investigational product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 December 2012
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	United States: 101
Country: Number of subjects enrolled	Italy: 18
Worldwide total number of subjects	119
EEA total number of subjects	18

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)	66
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 12 study centers, 8 in the US and 4 in Italy. 119 patients were recruited between December 2012 and January 2017.

Pre-assignment

Screening details:

A fresh core needle biopsy or fine needle aspiration could be collected during the screening period if archival tumor tissue biopsy samples were not available.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Dose Group

Arm description:

Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at dose levels from 25 mg every other day (QOD) - 200 mg daily (QD) on a 28-day schedule.

Arm title	Middle Dose Group

Arm description:

Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule.

Arm title	High Dose Group

Arm description:

Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule.

Arm title	Expanded Cohort Group

Arm description:

Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at the recommended phase 2 dose of 300 mg QD on a 28-day schedule.

Number of subjects in period 1	Low Dose Group	Middle Dose Group	High Dose Group
Started	29	13	19
Completed	0	0	0
Not completed	29	13	19
Physician decision	1	-	-
Consent withdrawn by subject	-	1	-
Radiographic disease progression	20	7	12
Adverse event, non-fatal	1	-	5
Other	1	1	1
Clinical disease progression	6	4	1
Study terminated by sponsor	-	-	-

Number of subjects in period 1	Expanded Cohort Group
Started	58
Completed	0
Not completed	58
Physician decision	2
Consent withdrawn by subject	1
Radiographic disease progression	29
Adverse event, non-fatal	10

Other	2
Clinical disease progression	13
Study terminated by sponsor	1

Baseline characteristics

Reporting groups	
Reporting group title	Low Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	
Reporting group title	Middle Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	
Reporting group title	High Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	
Reporting group title	Expanded Cohort Group
Reporting group description:	
Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	

Reporting group values	Low Dose Group	Middle Dose Group	High Dose Group
Number of subjects	29	13	19
Age categorical Units: Subjects			
Age < 65	19	4	8
Age >=65	10	9	11
Gender categorical Units: Subjects			
Female	17	9	11
Male	12	4	8
Race Units: Subjects			
Black or African American	3	1	2
White	24	11	16
Other	2	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	3
Not Hispanic or Latino	26	12	16

Reporting group values	Expanded Cohort Group	Total	
Number of subjects	58	119	
Age categorical Units: Subjects			
Age < 65	35	66	

Age >=65	23	53	

Gender categorical Units: Subjects			
Female	32	69	
Male	26	50	
Race Units: Subjects			
Black or African American	3	9	
White	54	105	
Other	1	5	
Ethnicity Units: Subjects			
Hispanic or Latino	2	9	
Not Hispanic or Latino	56	110	

End points

End points reporting groups

Reporting group title	Low Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	

Reporting group title	Middle Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	

Reporting group title	High Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	

Reporting group title	Expanded Cohort Group
Reporting group description:	
Patients who received derazantinib orally at the recommended Phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until documented progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria.	

Primary: Incidence of adverse events

End point title	Incidence of adverse events[1]
End point description:	
Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	
End point type	Primary
End point timeframe:	
Adverse events were collected and reported from the time of receiving first dose of derazantinib to the end of study assessment and follow-up period	

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: The primary objective of this study was to evaluate the safety and tolerability of derazantinib and the study was not powered for formal statistical analysis.

End point values	Low Dose Group	Middle Dose Group	High Dose Group	Expanded Cohort Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	13	19	58
Units: Number of subjects				
TEAE Grade 1	3	1	1	11
TEAE Grade 2	14	5	3	14
TEAE Grade 3	9	6	13	24
TEAE Grade 4	0	1	0	4
TEAE Grade 5	2	0	2	5
no TEAE	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response (ORR) per RECIST 1.1

End point title	Objective tumor response (ORR) per RECIST 1.1

End point description:

The number of patients with an objective tumor response, which included those with either a complete response (CR) or a partial response (PR). The objective response rate (ORR) was defined as the proportion of patients with a CR or PR.

End point type	Secondary

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

End point values	Low Dose Group	Middle Dose Group	High Dose Group	Expanded Cohort Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	13	19	58
Units: Number of subjects	0	0	1	5

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) per RECIST 1.1

End point title	Disease control rate (DCR) per RECIST 1.1

End point description:

The number of patients with tumor disease control, which included those with either a complete or partial tumor response, or a stable disease (SD). The disease control rate (DCR) was defined as the proportion of patients with CR, PR or SD.

End point type	Secondary

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

End point values	Low Dose Group	Middle Dose Group	High Dose Group	Expanded Cohort Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	13	19	58
Units: Number of subjects	8	4	7	32

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS was calculated as the time from the date of first dose until radiographic disease progression or death from any cause.

End point type	Secondary

End point timeframe:

At the End of Treatment visit (7 [+3] days after the last dose of derazantinib)

End point values	Low Dose Group	Middle Dose Group	High Dose Group	Expanded Cohort Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	13	19	58
Units: weeks				
median (confidence interval 95%)	8.3 (6.3 to 9.3)	15.3 (6.7 to 22.1)	8.1 (6.7 to 23.9)	17.4 (7.9 to 24.9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first administration of study medication up to 30 days after the last administration.	
Adverse event reporting additional description:	
Treatment-emergent adverse events and serious adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Low Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 25 mg QOD - 200 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.	
Reporting group title	Middle Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 250 mg QD - 325 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.	
Reporting group title	High Dose Group
Reporting group description:	
Patients who received derazantinib orally at dose levels from 400 mg QD - 425 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.	
Reporting group title	Expanded Cohort Group
Reporting group description:	
Patients who received derazantinib orally at the recommended phase 2 dose (RP2D) of 300 mg QD on a 28-day schedule until progression of disease (clinical or radiological), unacceptable toxicity, or another of the discontinuation criteria was documented.	

Serious adverse events	Low Dose Group	Middle Dose Group	High Dose Group
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 29 (31.03%)	2 / 13 (15.38%)	6 / 19 (31.58%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	2	0	2
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram abnormal			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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 injury cervical			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
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			
Chest pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Disease progression			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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			
Enterocutaneous fistula			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Odynophagia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Stomatitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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			
Dyspnoea			

subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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			
Abdominal wall abscess			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Appendicitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (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
Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
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	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (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
Hypokalaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (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	Expanded Cohort Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 58 (27.59%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	5		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram abnormal			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord injury cervical			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
General physical health deterioration			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Pyrexia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enterocutaneous fistula			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Odynophagia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Rectal haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Female genital tract fistula				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				

subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal wall abscess				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Low Dose Group	Middle Dose Group	High Dose Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)	13 / 13 (100.00%)	19 / 19 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 29 (10.34%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Haematoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypertension			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	4 / 19 (21.05%)
occurrences (all)	0	0	4
Hypotension			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	18 / 29 (62.07%)	8 / 13 (61.54%)	11 / 19 (57.89%)
occurrences (all)	24	14	18
Feeling abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Malaise			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	2
Mucosal inflammation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Performance status decreased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	2	2	0
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	4	0	1
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 29 (13.79%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	4	0	2
Dysphonia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	6 / 29 (20.69%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	6	0	1
Epistaxis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Hypoxia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	4
Laryngeal inflammation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nasal mucosal disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Psychiatric disorders			

Anxiety			
subjects affected / exposed	4 / 29 (13.79%)	3 / 13 (23.08%)	2 / 19 (10.53%)
occurrences (all)	5	3	3
Depression			
subjects affected / exposed	3 / 29 (10.34%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	4	0	1
Hallucination			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	2 / 19 (10.53%)
occurrences (all)	2	1	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	3 / 13 (23.08%)	4 / 19 (21.05%)
occurrences (all)	2	3	6
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 29 (24.14%)	7 / 13 (53.85%)	10 / 19 (52.63%)
occurrences (all)	10	10	14
Bilirubin conjugated increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 29 (27.59%)	2 / 13 (15.38%)	1 / 19 (5.26%)
occurrences (all)	8	2	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	4 / 29 (13.79%)	1 / 13 (7.69%)	4 / 19 (21.05%)
occurrences (all)	4	1	4
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 29 (17.24%)	2 / 13 (15.38%)	3 / 19 (15.79%)
occurrences (all)	6	2	3
Blood thyroid stimulating hormone			

increased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Blood urea increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	3
Breath sounds abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Electrocardiogram QT interval abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Visual acuity tests abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Excoriation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	3 / 19 (15.79%)
occurrences (all)	1	1	4
Head injury			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rib fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scratch			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Ichthyosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiomegaly			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Burning sensation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Clumsiness			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	5 / 19 (26.32%)
occurrences (all)	2	1	11
Dizziness postural			
subjects affected / exposed	0 / 29 (0.00%)	2 / 13 (15.38%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Dysgeusia			
subjects affected / exposed	3 / 29 (10.34%)	3 / 13 (23.08%)	3 / 19 (15.79%)
occurrences (all)	3	3	3
Head discomfort			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	3 / 19 (15.79%)
occurrences (all)	1	1	5
Hypoaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Neuropathy peripheral			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Tremor			

subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 29 (24.14%)	3 / 13 (23.08%)	0 / 19 (0.00%)
occurrences (all)	12	4	0
Leukopenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Lymphopenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hearing impaired			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	1 / 29 (3.45%)	2 / 13 (15.38%)	0 / 19 (0.00%)
occurrences (all)	2	2	0
Lacrimation increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vision blurred			

subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 29 (10.34%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	4	1	1
Abdominal pain			
subjects affected / exposed	2 / 29 (6.90%)	2 / 13 (15.38%)	1 / 19 (5.26%)
occurrences (all)	2	2	2
Abdominal pain upper			
subjects affected / exposed	1 / 29 (3.45%)	3 / 13 (23.08%)	0 / 19 (0.00%)
occurrences (all)	1	5	0
Ascites			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Cheilitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	5 / 29 (17.24%)	4 / 13 (30.77%)	7 / 19 (36.84%)
occurrences (all)	5	5	9
Diarrhoea			
subjects affected / exposed	6 / 29 (20.69%)	5 / 13 (38.46%)	9 / 19 (47.37%)
occurrences (all)	11	5	10
Dry mouth			
subjects affected / exposed	3 / 29 (10.34%)	1 / 13 (7.69%)	6 / 19 (31.58%)
occurrences (all)	3	1	8
Dyspepsia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 13 (0.00%)	3 / 19 (15.79%)
occurrences (all)	3	0	3

Flatulence			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 29 (0.00%)	2 / 13 (15.38%)	3 / 19 (15.79%)
occurrences (all)	0	2	4
Hiatus hernia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Intestinal obstruction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Lip disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lip pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	14 / 29 (48.28%)	8 / 13 (61.54%)	13 / 19 (68.42%)
occurrences (all)	18	14	15
Odynophagia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oral dysaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

Stomatitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Tongue disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	10 / 29 (34.48%)	2 / 13 (15.38%)	7 / 19 (36.84%)
occurrences (all)	11	5	7
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
Decubitus ulcer			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	2 / 29 (6.90%)	2 / 13 (15.38%)	5 / 19 (26.32%)
occurrences (all)	2	2	6
Erythema			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Nail discolouration			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Night sweats			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Onychomadesis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Photosensitivity reaction			

subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	3 / 29 (10.34%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	3	1	0
Scab			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scar			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin mass			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	2 / 19 (10.53%)
occurrences (all)	0	1	3
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Hydronephrosis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0

Micturition frequency decreased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	3 / 29 (10.34%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	5	0	1
Urinary incontinence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 29 (6.90%)	1 / 13 (7.69%)	2 / 19 (10.53%)
occurrences (all)	2	1	3
Muscle twitching			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	1

Cystitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Ear infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	12 / 29 (41.38%)	3 / 13 (23.08%)	6 / 19 (31.58%)
occurrences (all)	14	6	8
Dehydration			

subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	4 / 19 (21.05%)
occurrences (all)	2	0	5
Hypercalcaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	0	3
Hyperglycaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 13 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	6 / 29 (20.69%)	3 / 13 (23.08%)	1 / 19 (5.26%)
occurrences (all)	10	4	1
Hypochloraemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	3 / 29 (10.34%)	3 / 13 (23.08%)	2 / 19 (10.53%)
occurrences (all)	3	4	3
Hypomagnesaemia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Hyponatraemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 13 (0.00%)	3 / 19 (15.79%)
occurrences (all)	2	0	4
Hypophosphataemia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 13 (7.69%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 29 (0.00%)	0 / 13 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Non-serious adverse events	Expanded Cohort Group		
Total subjects affected by non-serious adverse events subjects affected / exposed	58 / 58 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all)	 2 / 58 (3.45%) 2		
Vascular disorders Flushing subjects affected / exposed occurrences (all) Haematoma subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 5 / 58 (8.62%) 5 0 / 58 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Discomfort subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Feeling abnormal subjects affected / exposed occurrences (all)	 13 / 58 (22.41%) 26 4 / 58 (6.90%) 4 0 / 58 (0.00%) 0 26 / 58 (44.83%) 40 0 / 58 (0.00%) 0		

Feeling hot subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Gait disturbance subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2		
Malaise subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1		
Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Oedema subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5		
Pain subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 2		
Performance status decreased subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 9		
Reproductive system and breast disorders			
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Cough				
subjects affected / exposed	7 / 58 (12.07%)			
occurrences (all)	7			
Dysphonia				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Dyspnoea				
subjects affected / exposed	5 / 58 (8.62%)			
occurrences (all)	5			
Epistaxis				
subjects affected / exposed	8 / 58 (13.79%)			
occurrences (all)	9			
Hypoxia				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Laryngeal inflammation				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Nasal congestion				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	4			
Nasal dryness				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Nasal mucosal disorder				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Oropharyngeal pain				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences (all)	3			
Productive cough				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Pulmonary congestion				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			

Respiratory failure subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Throat irritation subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Wheezing subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2		
Depression subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Hallucination subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	17 / 58 (29.31%) 31		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	17 / 58 (29.31%) 30		
Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Breath sounds abnormal			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT interval abnormal			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Visual acuity tests abnormal			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			

Arthropod bite subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Contusion subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2		
Excoriation subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1		
Fall subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1		
Head injury subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Joint injury subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Rib fracture subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Scratch subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Congenital, familial and genetic disorders Ichthyosis subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Cardiac disorders Cardiomegaly subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Tachycardia			

subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Burning sensation			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Clumsiness			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	15		
Dizziness postural			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	14		
Head discomfort			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	14		
Hypoaesthesia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		

Neuropathy peripheral			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	7		
Paraesthesia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	18		
Leukopenia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Hearing impaired			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Tinnitus			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	9		
Dry eye			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	8		
Lacrimation increased			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	14		
Visual acuity reduced			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Visual impairment			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Ascites			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Cheilitis			

subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	16 / 58 (27.59%)			
occurrences (all)	20			
Diarrhoea				
subjects affected / exposed	17 / 58 (29.31%)			
occurrences (all)	37			
Dry mouth				
subjects affected / exposed	19 / 58 (32.76%)			
occurrences (all)	23			
Dyspepsia				
subjects affected / exposed	6 / 58 (10.34%)			
occurrences (all)	7			
Flatulence				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences (all)	3			
Frequent bowel movements				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Hiatus hernia				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Intestinal obstruction				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Lip disorder				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Lip dry				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Lip pain				

subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	27 / 58 (46.55%)		
occurrences (all)	46		
Odynophagia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Oesophagitis			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Oral dysaesthesia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	6		
Tongue disorder			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	23 / 58 (39.66%)		
occurrences (all)	48		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	11		
Decubitus ulcer			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		

Erythema				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences (all)	2			
Nail discolouration				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Onychomadesis				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Photosensitivity reaction				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences (all)	3			
Rash				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	4			
Rash erythematous				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Rash macular				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	1			
Scab				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
Scar				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			

Skin fissures			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Skin mass			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	2		
Hydronephrosis			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Micturition frequency decreased			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Muscle twitching			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		

Muscular weakness			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	3		
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Oesophageal candidiasis			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Skin infection			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			

subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	15		
Dehydration			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Hypercalcaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	6		
Hyperphosphataemia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Hypochloraemia			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		

Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1		
Hyponatraemia subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 6		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	The original protocol was amended based on comments and/or requests from the FDA made during IND review.
21 June 2013	1. Based on the preliminary pharmacokinetic results obtained in patients enrolled in Cohorts 1-3, new derazantinib dose escalation guidelines were introduced. 2. The study design was changed so that patients would participate in a single treatment period of continuous dosing instead of participating in two treatment periods.
12 June 2014	1. A food-effect cohort was added 2. Inclusion / exclusion criteria were amended to permit patients to be enrolled in the Expanded Cohort 3. A specification was added with regard to collection of biopsies
04 November 2014	1. The recommended phase 2 dose was defined as 300 mg QD (fasted) 2. The eligibility requirements for the Expanded Cohort were clarified based on tumor type and/or tumor genomic profile
10 April 2015	1. The expanded tumor sub-cohorts were specified to include only patients with advanced solid tumors with FGFR genetic aberrations, including intrahepatic cholangiocarcinoma with FGFR2 gene fusion 2. The study title was changed to reflect the updated definition of tumor type and genomic profile 3. Changes were made to some inclusion and exclusion criteria 4. A clarification was added to dose delays / reduction for Grade 3-4 toxicity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28972963

http://www.ncbi.nlm.nih.gov/pubmed/30420614