



Clinical trial results:

A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113 Summary

EudraCT number	2011-005718-12
Trial protocol	ES
Global end of trial date	18 February 2020

Results information

Result version number	v2 (current)
This version publication date	06 March 2021
First version publication date	29 June 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	AP26113-11-101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01449461
WHO universal trial number (UTN)	U1111-1196-8197

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.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	18 February 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is 2-fold: initially, in the dose escalation phase, the goal is to determine the safety profile of orally administered AP26113, including: the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), recommended phase 2 dose (RP2D), and pharmacokinetic (PK) profile. Then, once the RP2D is established, an expansion phase will assess the preliminary anti-tumor activity of AP26113, both in non-small cell lung cancer (NSCLC) with ALK gene rearrangement (including participants with active brain metastases) or mutated EGFR, and in other cancers with abnormal targets against which AP26113 is active.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 130
Country: Number of subjects enrolled	Spain: 7
Worldwide total number of subjects	137
EEA total number of subjects	7

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)	98
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 9 investigative sites in the United States and Spain from 20 September 2011 to 18 February 2020.

Pre-assignment

Screening details:

Participants with advanced malignancies, all histologies other than leukemia were enrolled in dose-escalation and participants with non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) rearrangements were enrolled in dose expansion phase. Participants received brigatinib 30 mg - 300 mg, tablets, orally once daily or twice daily.

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	Brigatinib 30 mg QD/60 mg QD

Arm description:

Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Arm title	Brigatinib 90 mg QD
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Arm description:

Brigatinib 90 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Arm title	Brigatinib 120 mg QD/60 mg BID
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Arm description:

Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
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Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Arm title	Brigatinib 90 mg QD-180 mg QD
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Arm description:

Brigatinib 90 mg, tablets, orally, QD for 7 days followed by brigatinib 180 mg, orally, QD in Cycle 1 of 28 days followed by brigatinib 180 mg, orally, QD in cycle 2 and onward cycles of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Arm title	Brigatinib 180 mg QD/90 mg BID
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Arm description:

Brigatinib 180 mg, QD or 90 mg, BID, tablets, orally in each cycle of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Arm title	Brigatinib 240 mg QD/120 mg BID/300 mg QD
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Arm description:

Brigatinib 240 mg, QD or 120 mg, BID or 300 mg once daily, tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113 ALUNBRIG™
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets and capsules.

Number of subjects in period 1	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID
Started	6	18	18
Completed	0	0	0
Not completed	6	18	18
Adverse event, serious fatal	-	2	-
Physician decision	-	1	-
Documented Progressive disease	4	7	14
Adverse event, non-fatal	-	3	2
Withdrawn by Subject	-	1	-
Site Terminated by Sponsor	-	1	2
Clinical Progressive disease	2	2	-
Reason not Specified	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Brigatinib 90 mg QD-180 mg QD	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD
Started	32	48	15
Completed	0	0	0
Not completed	32	48	15
Adverse event, serious fatal	-	7	1
Physician decision	4	1	-
Documented Progressive disease	15	24	5
Adverse event, non-fatal	3	4	4
Withdrawn by Subject	-	2	1
Site Terminated by Sponsor	3	4	1
Clinical Progressive disease	3	4	2
Reason not Specified	3	2	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Brigatinib 30 mg QD/60 mg QD
Reporting group description: Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 90 mg QD
Reporting group description: Brigatinib 90 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 120 mg QD/60 mg BID
Reporting group description: Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 90 mg QD-180 mg QD
Reporting group description: Brigatinib 90 mg, tablets, orally, QD for 7 days followed by brigatinib 180 mg, orally, QD in Cycle 1 of 28 days followed by brigatinib 180 mg, orally, QD in cycle 2 and onward cycles of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 180 mg QD/90 mg BID
Reporting group description: Brigatinib 180 mg, QD or 90 mg, BID, tablets, orally in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 240 mg QD/120 mg BID/300 mg QD
Reporting group description: Brigatinib 240 mg, QD or 120 mg, BID or 300 mg once daily, tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).	

Reporting group values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID
Number of subjects	6	18	18
Age Categorical Units: participants			
Adults [18-64 years]	2	11	12
From 65 to 84 years	4	7	6
Age Continuous Units: years			
arithmetic mean	66.8	57.9	57.8
standard deviation	± 9.30	± 12.93	± 10.91
Gender, Male/Female Units: participants			
Female	3	12	13
Male	3	6	5
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	4	3
Black or African American	0	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	6	13	13
Unknown	0	0	0

Other	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	5	18	18
Eastern Cooperative Oncology Group (ECOG) Performance Score			
ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage [%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot carry on any selfcare, totally confined to bed or chair and 5=Dead.			
Units: Subjects			
ECOG Score: 0	0	3	3
ECOG Score: 1	6	15	15
ECOG Score: 2	0	0	0
Participants with Diagnosis of Cancer Type Units: Subjects			
NSCLC	3	16	18
Other	3	2	0
Number of Participants with Mutation Types Units: Subjects			
Anaplastic Lymphoma Kinase (ALK+)	1	16	6
Epidermal Growth Factor Receptor (EGFRm)	2	1	10
ROS Proto-oncogene 1 (ROS1+)	0	0	0
Other	3	1	2
Participants with Prior Chemotherapy Regimen Units: Subjects			
Prior Therapy=0	0	2	7
Prior Therapy=1	3	4	3
Prior Therapy=2	0	9	4
Prior Therapy >2	3	3	4
Participants with Prior Radiotherapy to Brain Units: Subjects			
No Prior Radiotherapy	6	13	17
Prior Radiotherapy	0	5	1
Region of Enrollment Units: Subjects			
United States	6	18	18
Spain	0	0	0
Study Specific Characteristic Time Since Diagnosis of Cancer Units: years			
arithmetic mean	2.48	3.33	2.41
standard deviation	± 3.303	± 2.184	± 1.346
Reporting group values	Brigatinib 90 mg QD-180 mg QD	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD

Number of subjects	32	48	15
Age Categorical			
Units: participants			
Adults [18-64 years]	25	39	9
From 65 to 84 years	7	9	6
Age Continuous			
Units: years			
arithmetic mean	55.7	53.9	58.5
standard deviation	± 11.41	± 11.10	± 15.60
Gender, Male/Female			
Units: participants			
Female	14	29	8
Male	18	19	7
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	3	5	2
Black or African American	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	0
White	27	39	12
Unknown	0	1	0
Other	1	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	31	47	15
Eastern Cooperative Oncology Group (ECOG) Performance Score			
ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage [%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot carry on any selfcare, totally confined to bed or chair and 5=Dead.			
Units: Subjects			
ECOG Score: 0	13	13	2
ECOG Score: 1	19	33	13
ECOG Score: 2	0	2	0
Participants with Diagnosis of Cancer Type			
Units: Subjects			
NSCLC	31	45	15
Other	1	3	0
Number of Participants with Mutation Types			
Units: Subjects			
Anaplastic Lymphoma Kinase (ALK+)	29	27	5
Epidermal Growth Factor Receptor (EGFRm)	3	18	9
ROS Proto-oncogene 1 (ROS1+)	0	3	1
Other	0	0	0
Participants with Prior Chemotherapy Regimen			

Units: Subjects			
Prior Therapy=0	12	12	3
Prior Therapy=1	6	17	2
Prior Therapy=2	8	10	5
Prior Therapy >2	6	9	5
Participants with Prior Radiotherapy to Brain			
Units: Subjects			
No Prior Radiotherapy	24	36	14
Prior Radiotherapy	8	12	1
Region of Enrollment			
Units: Subjects			
United States	32	41	15
Spain	0	7	0
Study Specific Characteristic Time Since Diagnosis of Cancer			
Units: years			
arithmetic mean	3.19	2.77	3.27
standard deviation	± 2.726	± 2.053	± 1.913

Reporting group values	Total		
Number of subjects	137		
Age Categorical			
Units: participants			
Adults [18-64 years]	98		
From 65 to 84 years	39		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: participants			
Female	79		
Male	58		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	17		
Black or African American	5		
Native Hawaiian or Other Pacific Islander	1		
White	110		
Unknown	1		
Other	1		
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	134		
Eastern Cooperative Oncology Group (ECOG) Performance Score			
ECOG assessed participant's performance status on a 5 point scale: 0 equals (=) fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, but ambulatory/able to carry out light or sedentary work; 2=ambulatory (greater than [>] 50 percentage			

[%] of waking hours [h]), capable of all self care, but unable to carry out any work activities; 3=capable of only limited self care, confined to bed/chair >50% of waking hours; 4= completely disabled, cannot carry on any selfcare, totally confined to bed or chair and 5=Dead.

Units: Subjects			
ECOG Score: 0	34		
ECOG Score: 1	101		
ECOG Score: 2	2		
Participants with Diagnosis of Cancer Type			
Units: Subjects			
NSCLC	128		
Other	9		
Number of Participants with Mutation Types			
Units: Subjects			
Anaplastic Lymphoma Kinase (ALK+)	84		
Epidermal Growth Factor Receptor (EGFRm)	43		
ROS Proto-oncogene 1 (ROS1+)	4		
Other	6		
Participants with Prior Chemotherapy Regimen			
Units: Subjects			
Prior Therapy=0	36		
Prior Therapy=1	35		
Prior Therapy=2	36		
Prior Therapy >2	30		
Participants with Prior Radiotherapy to Brain			
Units: Subjects			
No Prior Radiotherapy	110		
Prior Radiotherapy	27		
Region of Enrollment			
Units: Subjects			
United States	130		
Spain	7		
Study Specific Characteristic Time Since Diagnosis of Cancer			
Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Brigatinib 30 mg QD/60 mg QD
Reporting group description: Brigatinib 30 mg/60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 90 mg QD
Reporting group description: Brigatinib 90 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 120 mg QD/60 mg BID
Reporting group description: Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 90 mg QD-180 mg QD
Reporting group description: Brigatinib 90 mg, tablets, orally, QD for 7 days followed by brigatinib 180 mg, orally, QD in Cycle 1 of 28 days followed by brigatinib 180 mg, orally, QD in cycle 2 and onward cycles of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 180 mg QD/90 mg BID
Reporting group description: Brigatinib 180 mg, QD or 90 mg, BID, tablets, orally in each cycle of 28 days (Approximately up to 7.3 years).	
Reporting group title	Brigatinib 240 mg QD/120 mg BID/300 mg QD
Reporting group description: Brigatinib 240 mg, QD or 120 mg, BID or 300 mg once daily, tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received Brigatinib, tablets, orally, once daily (QD) in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 30 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 30 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 60 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 60 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 90 mg, tablets, orally, QD or twice daily (BID) in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 90 mg, tablets, orally, QD or BID in each cycle of 28 days (Approximately up to 7.3 years).	

Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 120 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 120 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 120 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 180 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 180 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 240 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 240 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 300 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 300 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 90 mg, tablets, orally, QD or BID in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 180 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 240 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 300 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 300 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 180 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	

Subject analysis set title	Dose Escalation Phase
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received brigatinib tablets, orally, QD starting at 30 mg in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 30 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 60 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 60 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 90 mg, tablets, orally, QD or BID in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 120 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	
Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis
Subject analysis set description: Brigatinib 240 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).	

Primary: Recommended Phase 2 Dose (RP2D) of Brigatinib

End point title	Recommended Phase 2 Dose (RP2D) of Brigatinib ^[1]
End point description:	
The RP2D is the maximum tolerated dose (MTD) or less. The MTD is defined as the dose range at which ≤ 1 of 6 evaluable participants experience dose limiting toxicities (DLT) within the first 28 days of treatment (end of Cycle 1). Safety population included all enrolled participants who received at least one dose of study drug. Here, 99.999 indicates R2PD for this study is a dose range.	
End point type	Primary
End point timeframe:	
28 days	

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: Statistical analysis was not available for this endpoint.

End point values	Brigatinib			
Subject group type	Subject analysis set			
Number of subjects analysed	137			
Units: mg				
arithmetic mean (full range (min-max))	99.999 (90 to 180)			

Statistical analyses

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^[2]
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End point description:

ORR is defined as the proportion of participants with complete response (CR) or partial response (PR) according to RECIST v1.1 after the initiation of study treatment. CR for target lesion: disappearance of all extranodal lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. CR for non-target lesion: Disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (<10mm short axis) and normalization of tumor marker level. PR: at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. Full analysis set (FAS) included all participants who received at least one dose of study drug. Participants with ALK and NSCLC were evaluated for this outcome measure. Here, n is the number of participants who were evaluable for specific category. 99999 indicates that no participants was analysed in this arm. Crzb=Crizotinib.

End point type	Primary
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End point timeframe:

From Screening and at 8-week intervals thereafter up to end of the study (up to 8.4 years)
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Notes:

[2] - 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: Statistical analysis was not available for this endpoint.

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	14	6	28
Units: percentage of participants				
number (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,13,5,25,23,4)	0 (0 to 0)	53.8 (25.1 to 80.8)	60.0 (14.7 to 94.7)	76.0 (54.9 to 90.6)
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	99999 (99999 to 99999)	100.0 (2.5 to 100.0)	100.0 (2.5 to 100.0)	100.0 (29.2 to 100.0)

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	5		
Units: percentage of participants				
number (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,13,5,25,23,4)	65.2 (42.7 to 83.6)	25.0 (0.6 to 80.6)		
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	100.0 (15.8 to 100.0)	100.0 (2.5 to 100.0)		

Statistical analyses

No statistical analyses for this end point
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Secondary: Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE)
End point description: An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. Safety population included all enrolled participants who received at least one dose of study drug.	
End point type	Secondary
End point timeframe: From first dose of study drug up to 30 days following the last dose of the study treatment or the investigator/participant decision to discontinue treatment, whichever occurs first (approximately up to 7.4 years)	

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	18	18	32
Units: participants	6	18	18	32

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	15		
Units: participants	48	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Tolerated Dose (MTD) Assessed in Dose Escalation Phase of the Study

End point title	Maximum Tolerated Dose (MTD) Assessed in Dose Escalation Phase of the Study
End point description: The MTD is defined as the highest dose at which ≤ 1 of 6 evaluable participants experience a DLT within the first 28 days of treatment (end of Cycle 1). Safety population included all enrolled participants who received at least one dose of study drug. Participants enrolled in the dose escalation phase were included in the analysis. Here, 99999 indicates that MTD criteria was not met.	
End point type	Secondary
End point timeframe: Up to Cycle 1 (28 days)	

End point values	Dose Escalation Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	66			
Units: mg				
number (not applicable)	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Dose Limiting Toxicities (DLTs) Assessed in Dose Escalation Phase of the Study

End point title	Number of Participants with Dose Limiting Toxicities (DLTs) Assessed in Dose Escalation Phase of the Study
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End point description:

DLT include any toxicity that is possibly, probably, or definitely drug-related. Toxicity grades will be defined by the NCI CTCAE v 4.0. DLTs are defined by the following: A) Non-hematologic toxicities: Any grade ≥ 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting < 3 days, and excluding alopecia. B) Hematologic toxicities: Febrile neutropenia not related to underlying disease (fever, $> 101^{\circ}\text{F}$; $\text{ANC} < 500$); Prolonged grade 4 neutropenia (> 7 days); Neutropenic infection: $\geq$ grade 3 neutropenia with $\geq$ grade 3 infection; Thrombocytopenia $\geq$ grade 3 with bleeding or grade 4 lasting ≥ 7 days. C) Missed $\geq 25\%$ of planned doses of brigatinib over 28 days due to treatment-related AEs in the first cycle. DLT-evaluable population included participants who received $\geq 75\%$ of planned study drug doses during Cycle 1.

End point type	Secondary
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End point timeframe:

Up to Cycle 1 (28 days)

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 90 mg	Brigatinib 120 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	5	3
Units: participants	0	0	0	0

End point values	Brigatinib 180 mg	Brigatinib 240 mg	Brigatinib 300 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	2	
Units: participants	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Brigatinib at Cycle 1 Day 1

End point title	Cmax: Maximum Observed Plasma Concentration for Brigatinib at Cycle 1 Day 1
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End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analyzed is the participants who were evaluable for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

End point type	Secondary
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End point timeframe:

Cycle 1 (28-days cycle): Day 1

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 120 mg	Brigatinib 90 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	11	50
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	125.6 (± 41.07)	406.3 (± 102)	793.7 (± 828.7)	493 (± 289.5)

End point values	Brigatinib 180 mg	Brigatinib 240 mg	Brigatinib 300 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	44	10	2	
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	1185 (± 607.6)	1515 (± 637.9)	895 (± 487.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Brigatinib at Cycle 2 Day 1

End point title	Cmax: Maximum Observed Plasma Concentration for Brigatinib at Cycle 2 Day 1
End point description: Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here number of participants analyzed is the participants with data available for analysis for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.	
End point type	Secondary
End point timeframe: Cycle 2 (28-days cycle): Day 1	

End point values	Brigatinib 180 mg	Brigatinib 300 mg	Brigatinib 30 mg	Brigatinib 60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	0 ^[3]	2	3
Units: ng/mL				
arithmetic mean (standard deviation)	1694.3 (± 1014.3)	()	249.50 (± 167.58)	491.67 (± 223.95)

Notes:

[3] - 99999 indicates that no participants was analysed in this arm.

End point values	Brigatinib 90 mg	Brigatinib 120 mg	Brigatinib 240 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	7	
Units: ng/mL				
arithmetic mean (standard deviation)	634.07 (± 310.05)	942.30 (± 472.33)	2280.0 (± 1308.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib at Cycle 1 Day 1

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib at Cycle 1 Day 1
End point description: Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analysed is the participants who were evaluable for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.	
End point type	Secondary
End point timeframe: Cycle 1 (28-days cycle): Day 1	

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 120 mg	Brigatinib 300 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	11	2
Units: hours				
median (full range (min-max))				
Tmax	3.9 (3.8 to 4.0)	1.0 (0.48 to 4.0)	2.0 (0.98 to 6.0)	4.05 (4.0 to 4.1)

End point values	Brigatinib 90 mg	Brigatinib 240 mg	Brigatinib 180 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	50	10	44	
Units: hours				
median (full range (min-max))				
Tmax	2.0 (0.48 to 24.0)	2.0 (1.0 to 4.0)	2.0 (0.60 to 25.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib at Cycle 2 Day 1

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib at Cycle 2 Day 1
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End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analysed is the participants with data available for analyses for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

End point type	Secondary
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End point timeframe:

Cycle 2 (28-days cycle): Day 1

End point values	Brigatinib 180 mg	Brigatinib 300 mg	Brigatinib 30 mg	Brigatinib 60 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	0 ^[4]	2	3
Units: hours				
median (full range (min-max))	2.10 (0.50 to 6.2)	(to)	2.49 (0.98 to 4.0)	1.10 (0.50 to 1.8)

Notes:

[4] - 99999 indicates that no participants was analysed in this arm.

End point values	Brigatinib 90 mg	Brigatinib 120 mg	Brigatinib 240 mg	
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Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	10	7	
Units: hours				
median (full range (min-max))	2.00 (0.98 to 8.0)	3.00 (0.50 to 6.1)	2.00 (1.0 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 hours post-dose for Brigatinib at Cycle 1 Day 1

End point title	AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 hours post-dose for Brigatinib at Cycle 1 Day 1
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End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analysed is the participants who were evaluable for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

End point type	Secondary
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End point timeframe:

Cycle 1 (28-days cycle): Day 1 multiple time points (up to 24 hours) post-dose

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 90 mg	Brigatinib 120 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	15	11
Units: h*ng/mL				
arithmetic mean (standard deviation)	1320.9 (± 576.29)	3900 (± 430.31)	5710.1 (± 3268.4)	9895.5 (± 11772)

End point values	Brigatinib 180 mg	Brigatinib 240 mg	Brigatinib 300 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	7	2	
Units: h*ng/mL				
arithmetic mean (standard deviation)	13204 (± 6306.9)	16800 (± 7571.1)	12356 (± 5869)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 hours post-dose for Brigatinib at Cycle 2 Day 1

End point title	AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 hours post-dose for Brigatinib at Cycle 2 Day 1
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End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analysed is the participants with data available for analyses for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

End point type	Secondary
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End point timeframe:

Cycle 2 (28-days cycle): Day 1 multiple time points (up to 24 hours) post-dose

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 90 mg	Brigatinib 120 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	15	10
Units: h*ng/mL				
arithmetic mean (standard deviation)	2689.0 ($\pm$ 1145.5)	5069.0 ($\pm$ 1664.7)	9142.1 ($\pm$ 4076.7)	13888 ($\pm$ 7011.4)

End point values	Brigatinib 180 mg	Brigatinib 240 mg	Brigatinib 300 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	7	0 ^[5]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	23478 ($\pm$ 14463)	30117 ($\pm$ 19921)	()	

Notes:

[5] - 99999 indicates that no participants was analysed in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2: Terminal Phase Elimination Half-life for Brigatinib at Cycle 2 Day 1

End point title	T1/2: Terminal Phase Elimination Half-life for Brigatinib at Cycle 2 Day 1
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End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, number of participants analysed is the participants with data available for this outcome measure. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point.

End point type	Secondary
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End point timeframe:

Cycle 2 (28-days cycle): Day 1

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 90 mg	Brigatinib 120 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	15	10
Units: hours				
arithmetic mean (standard deviation)	31.55 (± 2.758)	30.93 (± 5.873)	28.69 (± 10.06)	25.52 (± 7.958)

End point values	Brigatinib 180 mg	Brigatinib 240 mg	Brigatinib 300 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	7	0 ^[6]	
Units: hours				
arithmetic mean (standard deviation)	24.90 (± 7.437)	21.77 (± 4.007)	()	

Notes:

[6] - 99999 indicates that no participants was analysed in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response
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End point description:

Best overall response:percentage of participants with CR,PR,stable disease (SD)/progressive disease(PD) per RECISTv1.1 evaluated by investigator.CR(target lesion):disappearance of extranodal lesions,pathological lymph nodes decreased<10mm in short axis.CR(non-target lesion):disappearance of extranodal non-target lesions,lymph nodes(non-pathological size<10mm short axis),normalization of tumor marker level.PR:>=30%decrease in SLD of target lesions,using reference baseline sum diameters.PD (target lesion):SLD increased>=20%from smallest value,SLD must demonstrate absolute increase of>=5mm or development of any new lesion.PD(non-target lesion):unequivocal progression of existing non-target lesions.SD for neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.Full analysis set.ALK+NSCLC participants were evaluated.'n'=number of participants with data evaluable for specific category.99999=95%CI not estimable due to low number of participants with event.

End point type	Secondary
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End point timeframe:

Screening and at 8-week intervals thereafter up to end of the study (up to 8.4 years)

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	14	6	28
Units: percentage of participants				
number (confidence interval 95%)				
Prior Treatment with Crzb:CR(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	12.0 (2.5 to 31.2)
No Prior Treatment with Crzb:CR(n=1,1,1,3,2,1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	100.0 (2.5 to 100.0)	33.3 (0.8 to 90.6)
Prior Treatment with Crzb:PR(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	53.8 (25.1 to 80.8)	60.0 (14.7 to 94.7)	64.0 (42.5 to 82.0)
No Prior Treatment with Crzb:PR(n=1,1,1,3,2,1)	0.0 (0.0 to 0.0)	100.0 (2.5 to 100.0)	0.0 (0.0 to 0.0)	66.7 (9.4 to 99.2)
Prior Treatment with Crzb:SD(n=1,14,6,28,25,5)	100.0 (2.5 to 100.0)	23.1 (5.0 to 53.8)	0.0 (0.0 to 0.0)	12.0 (2.5 to 31.2)
No Prior Treatment with Crzb:SD(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Prior Treatment with Crzb:PD(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	8.0 (1.0 to 26.0)
No Prior Treatment with Crzb:PD(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	5		
Units: percentage of participants				
number (confidence interval 95%)				
Prior Treatment with Crzb:CR(n=1,14,6,28,25,5)	8.7 (1.1 to 28.0)	0.0 (0.0 to 0.0)		
No Prior Treatment with Crzb:CR(n=1,1,1,3,2,1)	0.0 (0.0 to 0.0)	100.0 (2.5 to 100.0)		
Prior Treatment with Crzb:PR(n=1,14,6,28,25,5)	56.5 (34.5 to 76.8)	25.0 (0.6 to 80.6)		
No Prior Treatment with Crzb:PR(n=1,1,1,3,2,1)	100.0 (15.8 to 100.0)	0 (0.0 to 0.0)		
Prior Treatment with Crzb:SD(n=1,14,6,28,25,5)	13.0 (2.8 to 33.6)	75.0 (19.4 to 99.4)		
No Prior Treatment with Crzb:SD(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		
Prior Treatment with Crzb:PD(n=1,14,6,28,25,5)	21.7 (7.5 to 43.7)	0.0 (0.0 to 0.0)		
No Prior Treatment with Crzb:PD(n=1,14,6,28,25,5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
End point description: DOR: interval from time of first CR/PR to first PD objectively documented/death. Participants who didn't progress/die censored at last response assessment. CR(target lesion): disappearance of extranodal lesions, pathological lymphnodes decreased <10mm in short axis. CR(non-target lesion): disappearance of extranodal non-target lesions, lymphnodes (non-pathological size <10mm short axis), normalization of tumor marker level. PR: ≥30% decrease in SLD of target lesions, using reference baseline sum diameters. PD (target lesion): SLD increased ≥20% from smallest value, SLD must demonstrate absolute increase of ≥5mm or development of any new lesion. PD(non-target lesion): unequivocal progression of existing non-target lesions. DOR calculated by Kaplan-Meier. FAS. Participants responded among those who had ALK, NSCLC were evaluated. n=participants with data evaluable for specific category. 99999, 999999=Median/95%CI not estimable due to low number of participants with event, respectively. 9999=no participants analysed.	
End point type	Secondary
End point timeframe: Screening and at 8-week intervals thereafter up to end of the study (up to 8.4 years)	

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	14	6	28
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,7,3,19,15,1)	99999 (99999 to 99999)	11.1 (3.8 to 16.7)	4.0 (3.7 to 29.5)	14.8 (7.9 to 25.1)
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	9999 (9999 to 9999)	30.4 (-999999 to 999999)	60.3 (-999999 to 999999)	52.0 (5.6 to 52.0)

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	5		
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,7,3,19,15,1)	20.4 (7.5 to 51.6)	29.7 (-999999 to 999999)		
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	20.8 (9.2 to 32.4)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

PFS: time interval from the date of the first dose of the study treatment until the first date at which disease progression is objectively documented, or death due to any cause, whichever occurs first. Disease progression for target lesion: SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) and SLD must also demonstrate an absolute increase of at least 5 mm or development of any new lesion. Disease progression for non-target lesion: Unequivocal progression of existing non-target lesions. (Subjective judgment by experienced reader). Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, overall number of participants analysed is the participants who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Screening and at 8-week intervals thereafter up to end of the study (up to 8.4 years)

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	15	17	21
Units: months				
median (confidence interval 95%)				
PFS	1.8 (1.0 to 5.5)	12.6 (0.9 to 47.9)	5.4 (0.8 to 63.9)	11.0 (0.5 to 53.6)

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	7		
Units: months				
median (confidence interval 95%)				
PFS	5.4 (0.1 to 69.9)	5.4 (1.8 to 31.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, overall number of participants analysed is the participants who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Screening and at 8-week intervals thereafter up to end of the study (up to 8.4 years)

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	11	12	17
Units: months				
median (confidence interval 95%)	5.3 (2.3 to 12.6)	11.6 (4.0 to 47.6)	7.3 (0.5 to 28.6)	17.9 (1.4 to 35.0)

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	11		
Units: months				
median (confidence interval 95%)	7.3 (0.1 to 55.0)	8.3 (3.3 to 22.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Objective Response Rate

End point title	Intracranial Objective Response Rate
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End point description:

Intracranial objective response rate is defined as the percentage of the participants with CR or PR in the intracranial CNS per modification of RECIST v1.1 after the initiation of study drug. CR for target lesion: disappearance of all extranodal lesions. CR for non-target lesion: disappearance of all extranodal non-target lesions and normalization of tumor marker level. PR: at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. Full analysis set. ALK+ NSCLC participants with measurable and non-measurable brain metastases at baseline were evaluated for this outcome measure. Here, n is the number of participants who were evaluable for specific category. Here 99999 indicates objective response rate was not estimable due to low number of participants with events. Meta.=Metastases.

End point type	Secondary
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End point timeframe:

Screening and at 8-week intervals thereafter (approximately up to 50 months)

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[7]	8	1	18
Units: percentage of participants				
number (confidence interval 95%)				
With Measurable Brain Meta.(n=0,2,0,5,7,1)	(to)	100 (15.8 to 100)	99999 (-99999 to 99999)	80 (28.4 to 99.5)
With Non-Measurable Brain Meta. (n=0,6,1,13,9,2)	(to)	16.7 (0.4 to 64.1)	100 (2.5 to 100)	46.2 (19.2 to 74.9)

Notes:

[7] - No participant was evaluated for this arm.

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: percentage of participants				
number (confidence interval 95%)				
With Measurable Brain Meta.(n=0,2,0,5,7,1)	42.9 (9.9 to 81.6)	100 (2.5 to 100)		
With Non-Measurable Brain Meta. (n=0,6,1,13,9,2)	44.4 (13.7 to 78.8)	50.0 (1.3 to 98.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intracranial Response

End point title	Duration of Intracranial Response
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End point description:

Intracranial duration of response is defined as the time interval from the time that the measurement criteria are first met for CR/PR in brain metastases (whichever is first recorded) until the first date that progressive disease is objectively documented or death due to any cause. Participants who did not progress nor die were censored at the last valid response assessment. Duration intracranial of response was calculated by Kaplan-Meier estimation. Full analysis set. ALK+ NSCLC participants with measurable and non-measurable brain metastases at baseline were evaluated for this outcome measure. Here 99999 indicates that upper/lower limits of CI were not reached due to low number of participants with events.

End point type	Secondary
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End point timeframe:

Screening and at 8-week intervals thereafter (approximately up to 50 months)

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[8]	8	1	18
Units: months				
median (confidence interval 95%)	(to)	12.9 (-99999 to 99999)	5.0 (-99999 to 99999)	11.4 (7.5 to 11.4)

Notes:

[8] - No participant was analysed in this arm

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: months				
median (confidence interval 95%)	29.2 (5.5 to 29.2)	11.3 (3.6 to 18.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Progression Free Survival (PFS)

End point title	Intracranial Progression Free Survival (PFS)
End point description:	
PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which disease progression in brain, or death due to any cause, whichever occurs first. Intracranial PFS was calculated by Kaplan-Meier estimation. Full analysis set. ALK+ NSCLC participants with measurable and only non-measurable brain metastases at baseline were evaluated for this outcome measure. Here 99999 indicates that median/upper limit of 95% CI was not reached due to low number of participants with events.	
End point type	Secondary
End point timeframe:	
Screening and at 8-week intervals thereafter (approximately up to 50 months)	

End point values	Brigatinib 30 mg QD/60 mg QD	Brigatinib 90 mg QD	Brigatinib 120 mg QD/60 mg BID	Brigatinib 90 mg QD-180 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[9]	8	1	18
Units: months				
median (confidence interval 95%)	(to)	36.8 (5.5 to 36.8)	6.7 (-99999 to 99999)	99999 (9.4 to 99999)

Notes:

[9] - No participant was analysed in this arm.

End point values	Brigatinib 180 mg QD/90 mg BID	Brigatinib 240 mg QD/120 mg BID/300 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: months				
median (confidence interval 95%)	14.4 (7.3 to 31.1)	7.3 (3.1 to 22.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Fatalities: From first dose up to End of Study (Up to 8.4 years). Serious and non-serious AEs: From first dose of study drug up to 30 days after last dose or investigator/participant decision to discontinue treatment (approximately up to 7.4 years)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	AP26113 30 mg QD/60 mg QD
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Reporting group description:

Brigatinib 30 mg/60 mg, tablets, orally, once daily QD in each cycle of 28 days (Approximately up to 7.3 years).

Reporting group title	AP26113 90 mg QD
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Reporting group description:

Brigatinib 90 mg, tablets, orally, QD in each cycle of 28 days (Approximately up to 7.3 years).

Reporting group title	AP26113 120 mg QD/60 mg BID
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Reporting group description:

Brigatinib 120 mg, once daily or 60 mg, BID, tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).

Reporting group title	AP26113 90 mg QD-180 mg QD
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Reporting group description:

Brigatinib 90 mg, tablets, orally, QD for 7 days followed by brigatinib 180 mg, orally, QD in Cycle 1 of 28 days followed by brigatinib 180 mg, orally, QD in cycle 2 and onward cycles of 28 days (Approximately up to 7.3 years).

Reporting group title	AP26113 180 mg QD/90 mg BID
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Reporting group description:

Brigatinib 180 mg, once daily or 90 mg, BID, tablets, orally in each cycle of 28 days (Approximately up to 7.3 years).

Reporting group title	AP26113 240 mg QD/120 mg BID/300 mg QD
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Reporting group description:

Brigatinib 240 mg, QD or 120 mg, BID or 300 mg QD, tablets, orally, in each cycle of 28 days (Approximately up to 7.3 years).

Serious adverse events	AP26113 30 mg QD/60 mg QD	AP26113 90 mg QD	AP26113 120 mg QD/60 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	10 / 18 (55.56%)	10 / 18 (55.56%)
number of deaths (all causes)	6	11	12
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Pericardial effusion malignant			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (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
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Malignant ascites			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 myeloid leukaemia recurrent			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Malignant pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Metastases to meninges			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Death			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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

Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Sudden death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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			
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Mental status changes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Suicidal ideation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Post procedural haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Radiation necrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Radiation pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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

Radiation associated cardiac failure subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Road traffic accident subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Atrial fibrillation subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Supraventricular tachycardia subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 congestive subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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 tamponade subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Tachycardia subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Angina unstable subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Cardio-respiratory arrest			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Central nervous system haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Cognitive disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Embolic stroke			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Haemorrhage intracranial			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 stroke			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Ischaemic stroke			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Nervous system disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Central nervous system lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Cerebral ischaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Status epilepticus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Eye disorders			
Blindness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Abdominal wall haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Bezoar			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Rectal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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			
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
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 pseudomonal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Cellulitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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 tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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			
Failure to thrive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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
Insulin resistance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (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
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (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	AP26113 90 mg QD-180 mg QD	AP26113 180 mg QD/90 mg BID	AP26113 240 mg QD/120 mg BID/300 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 32 (43.75%)	30 / 48 (62.50%)	11 / 15 (73.33%)
number of deaths (all causes)	17	25	11
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 32 (3.13%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	3 / 32 (9.38%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (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
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Malignant ascites			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Basal cell carcinoma			

subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia recurrent			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Malignant pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Metastases to meninges			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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			
Haematoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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			
Non-cardiac chest pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Influenza like illness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Sudden death			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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			
Hypoxia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	0 / 1	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (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
Pneumonitis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Haemoptysis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	4 / 15 (26.67%)
occurrences causally related to treatment / all	0 / 1	2 / 2	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea exertional			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Psychiatric disorders			

Mental status changes			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 32 (0.00%)	3 / 48 (6.25%)	0 / 15 (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
Suicidal ideation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Radiation necrosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (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
Radiation pneumonitis			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
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	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Radiation associated cardiac failure			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Road traffic accident			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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 tamponade			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Syncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Central nervous system haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Cognitive disorder			

subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Embolitic stroke			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (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 stroke			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Headache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Nervous system disorder			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Ataxia			

subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Central nervous system lesion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Dysarthria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Hydrocephalus			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Presyncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Status epilepticus			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Eye disorders			
Blindness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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			

Pancreatitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Bezoar			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Oesophageal compression			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
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 ulcer			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Intestinal obstruction			

subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Rash maculo-papular			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
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	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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

Pain in extremity			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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			
Pneumonia			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Device related sepsis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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 pseudomonal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Viral infection			

subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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 tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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			
Failure to thrive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Hyperglycaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Hyponatraemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (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
Insulin resistance			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (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
Dehydration			

subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (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

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

Non-serious adverse events	AP26113 30 mg QD/60 mg QD	AP26113 90 mg QD	AP26113 120 mg QD/60 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	17 / 18 (94.44%)	17 / 18 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Dysplastic naevus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	6 / 18 (33.33%)
occurrences (all)	0	2	7

Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vascular pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	9 / 18 (50.00%)	9 / 18 (50.00%)
occurrences (all)	2	12	10
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	4 / 18 (22.22%)
occurrences (all)	1	1	4
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	3	2
Pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	4	2
Chest discomfort			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Asthenia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Chills			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Axillary pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Feeling jittery			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Swelling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Temperature intolerance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Contrast media allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nipple pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Metrorrhagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	7 / 18 (38.89%)	6 / 18 (33.33%)
occurrences (all)	1	9	10
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	5 / 18 (27.78%)
occurrences (all)	0	4	6
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Oropharyngeal pain			

subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	3 / 18 (16.67%)
occurrences (all)	0	2	3
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sinus congestion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Sputum discoloured			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Dry throat			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hiccups			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Laryngeal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pleurisy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pulmonary hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory tract irritation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Bruxism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Anticipatory anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Nervousness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Stress			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	5 / 18 (27.78%)	5 / 18 (27.78%)
occurrences (all)	0	21	7
Lipase increased			

subjects affected / exposed	0 / 6 (0.00%)	5 / 18 (27.78%)	4 / 18 (22.22%)
occurrences (all)	0	23	7
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	7 / 18 (38.89%)
occurrences (all)	0	6	10
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	3 / 18 (16.67%)
occurrences (all)	0	4	4
Blood insulin increased			
subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	2 / 18 (11.11%)
occurrences (all)	0	7	5
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	4	2
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Blood testosterone decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	7	3
Blood bilirubin increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	3	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 6 (33.33%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Bacterial test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Heart rate increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Urinary sediment present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	4	13
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood sodium increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haematocrit decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Radiation neuropathy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Radiation pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Corneal abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Atrial flutter			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Cardiac failure congestive subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	8 / 18 (44.44%) 14	7 / 18 (38.89%) 12
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	5 / 18 (27.78%) 8	1 / 18 (5.56%) 2
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	2 / 18 (11.11%) 3
Paraesthesia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 18 (11.11%) 2	1 / 18 (5.56%) 1
Dysgeusia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	1 / 18 (5.56%) 1
Amnesia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Balance disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 18 (11.11%) 2	0 / 18 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Visual field defect subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Seizure			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Aphasia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Sinus headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Parosmia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Taste disorder			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	3	1
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	3 / 18 (16.67%)
occurrences (all)	0	1	3
Increased tendency to bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Deafness unilateral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Ear discomfort			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blepharospasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Asthenopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cataract cortical			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

Eyelid margin crusting subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Cataract subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Dyschromatopsia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	8 / 18 (44.44%) 9	9 / 18 (50.00%) 10
Diarrhoea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	8 / 18 (44.44%) 12	7 / 18 (38.89%) 12
Constipation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	6 / 18 (33.33%) 6	5 / 18 (27.78%) 6
Vomiting subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 18 (5.56%) 2	5 / 18 (27.78%) 6
Abdominal pain subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	1 / 18 (5.56%) 1	2 / 18 (11.11%) 2
Dry mouth subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 18 (16.67%) 3	0 / 18 (0.00%) 0
Abdominal distension			

subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	0	4	1
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	0	4	1
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	2	4
Cheilitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abdominal rigidity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lip swelling			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oesophageal irritation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Oesophageal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Aphthous ulcer			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Hyperaesthesia teeth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Enterocolitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Haematochezia			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	8
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	2
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	3	2
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Onychoclasia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	4	0
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Eczema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dermal cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Nail growth abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 2	0 / 18 (0.00%) 0
Actinic keratosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Rash papular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Eczema nummular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Rash erythematous subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 18 (11.11%) 2	2 / 18 (11.11%) 2
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	1 / 18 (5.56%) 1
Proteinuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	1 / 18 (5.56%) 1
Dysuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Renal failure subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Urinary retention			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	4 / 18 (22.22%)
occurrences (all)	1	3	5
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 18 (16.67%)	5 / 18 (27.78%)
occurrences (all)	1	3	6
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	1	7	1
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	3 / 18 (16.67%)	3 / 18 (16.67%)
occurrences (all)	1	7	7
Musculoskeletal chest pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Myalgia			

subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	0	5	1
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Arthritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Fracture pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Groin pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Osteopenia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	1	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	4 / 18 (22.22%)
occurrences (all)	0	1	4
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	4	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Conjunctivitis viral subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Diarrhoea infectious subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Folliculitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 2	0 / 18 (0.00%) 0
Infectious pleural effusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1
Laryngitis viral subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Nail infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Nasal herpes subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0
Onychomycosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 2	0 / 18 (0.00%) 0
Otitis externa subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 18 (0.00%) 0	0 / 18 (0.00%) 0
Paronychia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 18 (5.56%) 1	0 / 18 (0.00%) 0

Skin candida			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vaginal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear infection bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Kidney infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	5 / 18 (27.78%)	1 / 18 (5.56%)
occurrences (all)	0	7	1
Hypophosphataemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	9
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	1 / 18 (5.56%)
occurrences (all)	0	3	1
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Increased appetite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	9
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	AP26113 90 mg QD- 180 mg QD	AP26113 180 mg QD/90 mg BID	AP26113 240 mg QD/120 mg BID/300 mg QD
Total subjects affected by non-serious adverse events			

subjects affected / exposed	31 / 32 (96.88%)	45 / 48 (93.75%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Melanocytic naevus			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Basal cell carcinoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dysplastic naevus			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 32 (34.38%)	10 / 48 (20.83%)	1 / 15 (6.67%)
occurrences (all)	17	14	1
Hypotension			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Deep vein thrombosis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vascular pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Hot flush			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 32 (50.00%)	19 / 48 (39.58%)	12 / 15 (80.00%)
occurrences (all)	16	26	14
Oedema peripheral			
subjects affected / exposed	6 / 32 (18.75%)	5 / 48 (10.42%)	4 / 15 (26.67%)
occurrences (all)	6	8	4
Pyrexia			
subjects affected / exposed	6 / 32 (18.75%)	7 / 48 (14.58%)	2 / 15 (13.33%)
occurrences (all)	8	9	2
Pain			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	4	3	1
Chest discomfort			
subjects affected / exposed	3 / 32 (9.38%)	5 / 48 (10.42%)	2 / 15 (13.33%)
occurrences (all)	3	5	3
Non-cardiac chest pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	3 / 15 (20.00%)
occurrences (all)	1	3	3
Influenza like illness			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	6	7	1
Asthenia			
subjects affected / exposed	1 / 32 (3.13%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	1	7	1
Chills			
subjects affected / exposed	3 / 32 (9.38%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	3	2	5
Gait disturbance			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	2	4	0
Peripheral swelling			

subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Chest pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Thirst			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Feeling abnormal			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Feeling jittery			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Mucosal inflammation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 32 (0.00%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	3	0

Contrast media allergy subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Reproductive system and breast disorders			
Vulvovaginal dryness subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Nipple pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	1 / 15 (6.67%) 1
Metrorrhagia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	13 / 32 (40.63%) 20	14 / 48 (29.17%) 18	8 / 15 (53.33%) 10
Dyspnoea subjects affected / exposed occurrences (all)	7 / 32 (21.88%) 8	10 / 48 (20.83%) 14	4 / 15 (26.67%) 4
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	4 / 48 (8.33%) 4	1 / 15 (6.67%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	5 / 48 (10.42%) 5	2 / 15 (13.33%) 2
Epistaxis subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	4 / 48 (8.33%) 4	2 / 15 (13.33%) 2
Productive cough subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	5 / 48 (10.42%) 6	0 / 15 (0.00%) 0
Nasal congestion			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Haemoptysis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Hypoxia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	1	3	3
Rhinorrhoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	3	0
Sinus congestion			
subjects affected / exposed	4 / 32 (12.50%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	5	1	0
Dysphonia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	1	3	1
Rhinitis allergic			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Sputum discoloured			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Dry throat			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Hiccups			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Laryngeal inflammation			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Pleuritic pain			

subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Throat irritation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Nasal dryness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pleurisy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pulmonary hypertension			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory tract irritation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Upper-airway cough syndrome			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 32 (18.75%)	6 / 48 (12.50%)	3 / 15 (20.00%)
occurrences (all)	6	6	3
Anxiety			
subjects affected / exposed	5 / 32 (15.63%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	5	2	1

Depression			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	4	3	0
Bruxism			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Anticipatory anxiety			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Disorientation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Stress			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Investigations			
Amylase increased			
subjects affected / exposed	10 / 32 (31.25%)	9 / 48 (18.75%)	3 / 15 (20.00%)
occurrences (all)	28	17	6
Lipase increased			
subjects affected / exposed	12 / 32 (37.50%)	6 / 48 (12.50%)	3 / 15 (20.00%)
occurrences (all)	25	26	5
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 32 (31.25%)	9 / 48 (18.75%)	2 / 15 (13.33%)
occurrences (all)	13	17	2
Alanine aminotransferase increased			
subjects affected / exposed	6 / 32 (18.75%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	14	5	1
Blood insulin increased			

subjects affected / exposed	4 / 32 (12.50%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	8	9	0
Weight decreased			
subjects affected / exposed	5 / 32 (15.63%)	6 / 48 (12.50%)	2 / 15 (13.33%)
occurrences (all)	6	6	3
Blood creatinine increased			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	5	4	1
Lymphocyte count decreased			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Weight increased			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	4	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Blood testosterone decreased			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	2	5	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	3	0
Activated partial thromboplastin time prolonged			

subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	6	3	1
Bacterial test positive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Heart rate increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Urinary sediment present			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 32 (12.50%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	10	8	3
Blood alkaline phosphatase decreased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Blood phosphorus decreased			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood sodium increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Haematocrit decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Procedural pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Radiation neuropathy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Radiation pneumonitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	4 / 32 (12.50%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	4	2	1
Arthropod bite			

subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Skin laceration			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Corneal abrasion			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Joint dislocation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Palpitations			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Sinus bradycardia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Atrial flutter			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 32 (43.75%)	18 / 48 (37.50%)	6 / 15 (40.00%)
occurrences (all)	20	23	9
Dizziness			

subjects affected / exposed	5 / 32 (15.63%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	6	4	2
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 32 (18.75%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	6	3	0
Paraesthesia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	2	4	1
Dysgeusia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	1	3	1
Tremor			
subjects affected / exposed	3 / 32 (9.38%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Amnesia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	2	3	0
Balance disorder			
subjects affected / exposed	2 / 32 (6.25%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	3	5	0
Hypoaesthesia			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	8	1
Visual field defect			
subjects affected / exposed	0 / 32 (0.00%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	0	5	1
Seizure			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	2	3	3
Aphasia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	1	3	1
Disturbance in attention			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Dysarthria			

subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Sinus headache			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Burning sensation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Parosmia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Ataxia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Neuropathy peripheral			

subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Dizziness postural subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 8	4 / 48 (8.33%) 8	3 / 15 (20.00%) 3
Increased tendency to bruise subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 48 (4.17%) 2	1 / 15 (6.67%) 1
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 48 (2.08%) 1	1 / 15 (6.67%) 1
Deafness unilateral subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Ear discomfort subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Ear pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 6	5 / 48 (10.42%) 6	0 / 15 (0.00%) 0
Dry eye			

subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	2
Blepharospasm			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Photopsia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Asthenopia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cataract cortical			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eyelid margin crusting			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Eyelid oedema			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dyschromatopsia			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eye swelling			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 32 (50.00%)	33 / 48 (68.75%)	8 / 15 (53.33%)
occurrences (all)	21	45	11
Diarrhoea			
subjects affected / exposed	17 / 32 (53.13%)	21 / 48 (43.75%)	8 / 15 (53.33%)
occurrences (all)	22	47	22
Constipation			
subjects affected / exposed	9 / 32 (28.13%)	8 / 48 (16.67%)	4 / 15 (26.67%)
occurrences (all)	13	10	4
Vomiting			
subjects affected / exposed	9 / 32 (28.13%)	19 / 48 (39.58%)	5 / 15 (33.33%)
occurrences (all)	18	34	5
Abdominal pain			
subjects affected / exposed	6 / 32 (18.75%)	5 / 48 (10.42%)	2 / 15 (13.33%)
occurrences (all)	6	6	5
Dry mouth			
subjects affected / exposed	5 / 32 (15.63%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	5	2	2
Abdominal distension			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	2	4	0
Abdominal discomfort			
subjects affected / exposed	2 / 32 (6.25%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	2	5	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	3 / 15 (20.00%)
occurrences (all)	4	3	3
Dyspepsia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	3	1	1

Dysphagia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	3 / 15 (20.00%)
occurrences (all)	2	2	3
Flatulence			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Stomatitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Abdominal rigidity			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Abnormal faeces			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Lip swelling			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oesophageal irritation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oesophageal pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Hypoaesthesia oral subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	1 / 15 (6.67%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 4	6 / 48 (12.50%) 6	0 / 15 (0.00%) 0
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 48 (4.17%) 2	0 / 15 (0.00%) 0
Hyperaesthesia teeth subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	1 / 48 (2.08%) 1	1 / 15 (6.67%) 1
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Eruption subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Enterocolitis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	3 / 48 (6.25%) 3	0 / 15 (0.00%) 0
Photosensitivity reaction subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	5 / 48 (10.42%) 5	0 / 15 (0.00%) 0
Pruritus			

subjects affected / exposed	7 / 32 (21.88%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	7	3	0
Dry skin			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	4	3	0
Night sweats			
subjects affected / exposed	0 / 32 (0.00%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Dermatitis acneiform			
subjects affected / exposed	3 / 32 (9.38%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Alopecia			
subjects affected / exposed	0 / 32 (0.00%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	0	5	2
Hyperhidrosis			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	2	3	2
Onychoclasia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Rash pruritic			
subjects affected / exposed	3 / 32 (9.38%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	4	2	0
Dermatitis contact			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Erythema			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Pain of skin			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Skin disorder			

subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dermal cyst			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Dermatitis atopic			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Nail disorder			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Nail growth abnormal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Actinic keratosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Eczema nummular			

subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Rash erythematous subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	4 / 48 (8.33%) 7	0 / 15 (0.00%) 0
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	4 / 48 (8.33%) 4	0 / 15 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	1 / 48 (2.08%) 1	2 / 15 (13.33%) 2
Haematuria subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 4	2 / 48 (4.17%) 2	0 / 15 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 48 (4.17%) 2	1 / 15 (6.67%) 1
Renal failure subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	2 / 48 (4.17%) 2	0 / 15 (0.00%) 0
Hyperthyroidism			

subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	8 / 32 (25.00%)	13 / 48 (27.08%)	3 / 15 (20.00%)
occurrences (all)	9	15	7
Back pain			
subjects affected / exposed	11 / 32 (34.38%)	10 / 48 (20.83%)	1 / 15 (6.67%)
occurrences (all)	14	13	1
Musculoskeletal pain			
subjects affected / exposed	3 / 32 (9.38%)	8 / 48 (16.67%)	3 / 15 (20.00%)
occurrences (all)	3	10	3
Arthralgia			
subjects affected / exposed	10 / 32 (31.25%)	10 / 48 (20.83%)	0 / 15 (0.00%)
occurrences (all)	15	11	0
Pain in extremity			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	2 / 15 (13.33%)
occurrences (all)	3	4	4
Musculoskeletal chest pain			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	5	3	1
Joint swelling			
subjects affected / exposed	5 / 32 (15.63%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	6	2	0
Myalgia			
subjects affected / exposed	6 / 32 (18.75%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	7	3	1
Bone pain			
subjects affected / exposed	1 / 32 (3.13%)	6 / 48 (12.50%)	0 / 15 (0.00%)
occurrences (all)	1	6	0
Musculoskeletal discomfort			
subjects affected / exposed	3 / 32 (9.38%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	3	2	0
Flank pain			

subjects affected / exposed	3 / 32 (9.38%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Muscular weakness			
subjects affected / exposed	5 / 32 (15.63%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	5	1	0
Pain in jaw			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Arthritis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Fracture pain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Limb discomfort			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	3	0	2
Osteopenia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	12 / 32 (37.50%) 16	7 / 48 (14.58%) 9	3 / 15 (20.00%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 7	7 / 48 (14.58%) 10	1 / 15 (6.67%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 13	9 / 48 (18.75%) 12	1 / 15 (6.67%) 2
Sinusitis subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 7	3 / 48 (6.25%) 4	4 / 15 (26.67%) 5
Pneumonia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 48 (2.08%) 1	2 / 15 (13.33%) 2
Bronchitis subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	0 / 48 (0.00%) 0	2 / 15 (13.33%) 3
Influenza subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 48 (4.17%) 4	1 / 15 (6.67%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	0 / 15 (0.00%) 0
Conjunctivitis viral subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	1 / 15 (6.67%) 1
Diarrhoea infectious subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	1 / 15 (6.67%) 2

Folliculitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Fungal skin infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infectious pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Laryngitis viral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nail infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nasal herpes			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Paronychia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin candida			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	4	0

Gastroenteritis viral subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 48 (0.00%) 0	1 / 15 (6.67%) 1
Herpes zoster subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	2 / 48 (4.17%) 2	0 / 15 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 48 (2.08%) 1	1 / 15 (6.67%) 1
Ear infection bacterial subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Kidney infection subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	1 / 15 (6.67%) 1
Oral herpes subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 48 (0.00%) 0	0 / 15 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	10 / 32 (31.25%) 10	12 / 48 (25.00%) 13	5 / 15 (33.33%) 5
Hypophosphataemia subjects affected / exposed occurrences (all)	7 / 32 (21.88%) 11	4 / 48 (8.33%) 6	1 / 15 (6.67%) 1
Hypomagnesaemia subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	2 / 48 (4.17%) 3	3 / 15 (20.00%) 3
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	5 / 48 (10.42%) 6	3 / 15 (20.00%) 3
Hyponatraemia			

subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	9	3	2
Dehydration			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Hyperglycaemia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Increased appetite			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Gout			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2011	• Provided guidance on the medications that should be avoided, due to their risk of Torsades de Pointes. • Stated that potent CYP2C8 inhibitors and inducers should be avoided as in vitro data on brigatinib indicate this is a major enzyme responsible for metabolism of the drug. • Specified that drug-related toxicities include any toxicity that is possibly, probably, or definitely drug-related.
21 February 2012	• Made minor typographical and administrative changes outlined in the administrative letter sent to sites dated 20 October 2011. • Provided clarification to the study sites on the intent of the protocol. • Included monitoring of testosterone levels in men and thyroid-stimulating hormone in all participants during the course of the study • Allowed flexibility in the amount of tumor tissue needed for study entry. • Included time point windows for PK sampling. • Added a baseline blood sample to aid analysis of genetic alterations in tumor tissue.
17 September 2012	• Made minor adjustments to the sponsor representative names and contact information. • Clarified the exclusion criterion regarding previous usage of TKIs to specify that this referred to FDA-approved TKIs and that they were allowed only for participants free of treatment-related toxicity that might have confounded safety evaluations. • Altered the exclusion criterion regarding brain metastases to exclude participants with CNS metastases that were symptomatic and/or required steroid or anticonvulsant use, but clarified that CNS metastases might have been permissible after discussion with the sponsor if they were present without symptoms and/or neurological deficits in the physical examination or, in the case of suspected meningeal involvement, by a negative lumbar puncture prior to study entry. • Included an additional requirement that intra-patient dose escalation could occur only if Cycle 2 PK samples were drawn per protocol to aid PK data analysis and reduce variability between Cycle 1 and Cycle 2 PK datasets. • Allowed usage of concomitant anticancer medications that were local therapies used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator. • Added a 1-hour time point for triplicate ECGs for Cycle, 2 Day 1. • Added a pre-dose blood draw for PK for Cycle 3, Day 1; extended the window of time to ± 60 minutes at the 24- and 48-hour time points (versus ± 20 minutes); and added detail to the PK section within the text under Schedule of Events to match what was mentioned in the table footnotes. • Specified that if tumor assessments were performed and results were available, they were to be documented as part of the follow-up assessments. • Extended the contraception period to 120 days for males to account for spermatogenesis and added language to the pregnancy section to be consistent with other sponsor protocols.
30 November 2012	• Modified protocol eligibility criteria and added a trial procedure to allow for further improvement of safety evaluations. • Clarified twice daily dosing regimen. • Measured additional biomarkers to examine circulating tumor DNA and gain additional information on the molecular profile of participants' tumors.

22 May 2013	• Modified protocol eligibility criteria to allow for inclusion of another expansion phase cohort of NSCLC participants with active brain metastases. • Modified protocol eligibility criteria to further clarify the type of ALK and EGFR participants to be enrolled. • Updated brain imaging assessments and tissue collection method descriptions.
20 December 2013	• Updated the sponsor representative name and information • Adjusted the number of participants predicted to be enrolled in Cohort 2 and clarified that additional dosing strategies might have been evaluated in the expansion phase of the trial to gather additional safety and efficacy data at a dose below the current RP2D. • Updated the information regarding drugs with a known risk of Torsades de Pointes • Updated the department name of Pharmacovigilance and Risk Management.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported