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	

Results information

Result version number	v1
This version publication date	29 June 2017
First version publication date	29 June 2017

Trial information

Trial identification

Sponsor protocol code	AP26113-11-101

Additional study identifiers

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

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 Organization: Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science Organization: Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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	Interim
Date of interim/final analysis	16 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2015
Global end of trial reached?	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	Efficacy, Safety
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	Spain: 7
Country: Number of subjects enrolled	United States: 130
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 up to clinical cut-off date 16 November 2015. Study is ongoing.

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 44.4 months).

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

Dosage and administration details:

Brigatinib tablets and capsules

Arm title	Brigatinib 90 mg QD

Arm description:

Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113
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

Arm description:

Brigatinib 120 mg, once daily or 60 mg, twice daily (BID), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

Arm type	Experimental

Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113
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

Arm description:

Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113
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

Arm description:

Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113
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

Arm description:

Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	AP26113
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	-	1	-
Clinical progressive disease	2	1	-
Adverse event, non-fatal	-	3	2
Ongoing	-	6	2
Documented progressive disease	4	6	14
Reason not specified	-	1	-

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	-	4	1
Clinical progressive disease	-	3	3
Adverse event, non-fatal	3	3	3
Ongoing	15	17	2
Documented progressive disease	11	21	5
Reason not specified	3	-	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 44.4 months).	
Reporting group title	Brigatinib 90 mg QD
Reporting group description:	
Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).	
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 44.4 months).	
Reporting group title	Brigatinib 90 mg QD-180 mg QD
Reporting group description:	
Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days.	
Reporting group title	Brigatinib 180 mg QD/90 mg BID
Reporting group description:	
Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).	
Reporting group title	Brigatinib 240 mg QD/120 mg BID/300 mg QD
Reporting group description:	
Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).	

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: Subjects			
18 – 64 years	2	11	12
≥65 years	4	7	6
Age Continuous Units: years			
arithmetic mean	66.8	57.9	57.8
standard deviation	± 9.3	± 12.93	± 10.91
Gender, Male/Female Units: Subjects			
Female	3	6	5
Male	3	12	13
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=3	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: Subjects			
18 – 64 years	25	39	9
≥65 years	7	9	6
Age Continuous Units: years			
arithmetic mean	55.7	53.9	58.5
standard deviation	± 11.41	± 11.1	± 15.6
Gender, Male/Female Units: Subjects			
Female	18	19	7
Male	14	29	8
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=3	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: Subjects			
18 – 64 years	98		
≥65 years	39		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	58		
Male	79		
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=3	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 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 44.4 months).	
Reporting group title	Brigatinib 90 mg QD
Reporting group description:	
Brigatinib 90 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).	
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 44.4 months).	
Reporting group title	Brigatinib 90 mg QD-180 mg QD
Reporting group description:	
Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by brigatinib 180 mg, orally once daily in Cycle 1 of 28 days followed by brigatinib 180 mg, orally once daily in cycle 2 and onward cycles of 28 days.	
Reporting group title	Brigatinib 180 mg QD/90 mg BID
Reporting group description:	
Brigatinib 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).	
Reporting group title	Brigatinib 240 mg QD/120 mg BID/300 mg QD
Reporting group description:	
Brigatinib 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily, tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).	
Subject analysis set title	Brigatinib
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received Brigatinib, tablets, orally, once daily in each cycle of 28 days.	
Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).	
Subject analysis set title	Brigatinib 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Brigatinib 60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).	
Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).	
Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).	
Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 300 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 300 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 300 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 300 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Dose Escalation Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received brigatinib tablets, orally, once daily (QD) starting at 30 mg in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 30 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 30 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 60 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 60 mg, tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 90 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, once daily or twice daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 120 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 120 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 180 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 180 mg, tablets, orally once daily in each cycle of 28 days (approximately, up to 44.4 months).

Subject analysis set title	Brigatinib 240 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Brigatinib 240 mg, tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Primary: Recommended Phase 2 Dose of AP26113

End point title	Recommended Phase 2 Dose of AP26113[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 not reported 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

No statistical analyses for this end point

Primary: Objective Response Rate (ORR)

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

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 participant was analyzed in this arm. Crzb=Crizotinib.

End point type	Primary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (approximately up to 50 months)

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 not reported 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)	100 (2.5 to 100)	76.9 (46.2 to 95)	60 (14.7 to 94.7)	80 (59.3 to 93.2)
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	99999 (99999 to 99999)	100 (2.5 to 100)	100 (2.5 to 100)	100 (29.2 to 100)

End point values	Brigatinib 180 mg QD/90 mg	Brigatinib 240 mg QD/120 mg		

	BID	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)	50 (6.8 to 93.2)		
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	100 (15.8 to 100)	100 (2.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Objective Response Rate

End point title	Intracranial Objective Response Rate

End point description:

Intracranial objective response rate is defined as the proportion 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 only 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. 99999 indicates No participant was evaluated for this arm. Meta.=Metastases.

End point type	Secondary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (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[3]	8	1	18
Units: percentage of participants				
number (confidence interval 95%)				
With Measurable Brain Metastases (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:

[3] - 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				

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). Evaluable participants must complete at least 75% of their planned doses, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD. Safety population included all enrolled participants who received at least one dose of study drug. MTD was not formally determined. 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

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°F; ANC<500); Prolonged grade 4 neutropenia (> 7 days); Neutropenic infection: ≥ grade 3 neutropenia with ≥ grade 3 infection; Thrombocytopenia ≥ grade 3 with bleeding or grade 4 lasting ≥ 7 days. C) Missed ≥ 25% of planned doses of brigatinib over 28 days due to treatment-related AEs in the first cycle. Safety population included all enrolled participants who received at least one dose of study drug.

End point type	Secondary

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

End point title	Cmax: Maximum Observed Plasma Concentration for Brigatinib

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here number of participant analyzed is the participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Cycle 1 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	3	3	50	11
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	125.6 (± 41.07)	406.3 (± 102)	493 (± 289.5)	793.7 (± 828.7)

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 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point. Here 99999 indicates that standard deviation was not calculated.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 300 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	2	50
Units: hours				
arithmetic mean (standard deviation)				
Tmax	3.9 (± 99999)	1.83 (± 1.9)	4.05 (± 99999)	3.26 (± 4.53)

End point values	Brigatinib 120 mg	Brigatinib 240 mg	Brigatinib 180 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	11	10	44	
Units: hours				
arithmetic mean (standard deviation)				
Tmax	2.78 (± 1.7)	2.22 (± 1.02)	2.99 (± 3.77)	

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 AP26113

End point title	AUC(0-24): Area Under the Plasma Concentration-Time Curve

	From Time 0 to 24 hours post-dose for AP26113

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. 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 Day 1, 8, 15 and 22 pre-dose and Day 1 multiple timepoints (up to 48 hours) post-dose; Cycle 2 Day 1 and 3 pre-dose and Day 1 multiple time points (up to 48 hours) post-dose

End point values	Brigatinib 30 mg	Brigatinib 60 mg	Brigatinib 300 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	2	11
Units: h*ng/mL				
arithmetic mean (standard deviation)	1320.9 (± 576.29)	3900 (± 430.31)	7571.1 (± 99999)	9895.5 (± 11772)

End point values	Brigatinib 180 mg	Brigatinib 90 mg	Brigatinib 240 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	44	15	7	
Units: h*ng/mL				
arithmetic mean (standard deviation)	13204 (± 6306.9)	5710.1 (± 3268.4)	16800 (± 7571.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Phase Elimination Half-life (T1/2) for Brigatinib

End point title	Terminal Phase Elimination Half-life (T1/2) for Brigatinib

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Participants of brigatinib 90 mg QD-180 mg QD arm were included as per treatment received at each time point. Here, 99999 indicates that standard deviation was not calculated.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1

End point values	Brigatinib 60 mg	Brigatinib 180 mg	Brigatinib 90 mg	Brigatinib 240 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	63	15	7
Units: hours				
arithmetic mean (standard deviation)	30.93 (± 5.873)	24.9 (± 7.437)	28.69 (± 10.06)	21.77 (± 4.007)

End point values	Brigatinib 30 mg	Brigatinib 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	10		
Units: hours				
arithmetic mean (standard deviation)	31.55 (± 99999)	25.52 (± 7.958)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

Best overall response is defined as proportion of participants with CR, PR, stable disease (SD) or progressive disease (PD) as per of RECIST v1.1 as evaluated by investigator. Disease progression for target lesion: SLD increased by at least 20% from smallest value on study and SLD must also demonstrate an absolute increase of at least 5 mm or development of any new lesion. PD for 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. Participants with ALK and NSCLC were evaluated for this outcome measure. Here 99999 indicates 95% CI was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (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	1	13	5	25
Units: percentage of participants				
number (confidence interval 95%)				
Complete Response	0 (-99999 to 99999)	0 (-99999 to 99999)	0 (-99999 to 99999)	8 (1 to 26)
Partial Response	100 (2.5 to 100)	76.9 (46.2 to 95)	60 (14.7 to 94.7)	72 (50.6 to 87.9)
Stable Disease	0 (-99999 to 99999)	0 (-99999 to 99999)	0 (-99999 to 99999)	8 (1 to 26)

Progressive Disease	0 (-99999 to 99999)	0 (-99999 to 99999)	0 (-99999 to 99999)	8 (1 to 26)

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	23	4		
Units: percentage of participants				
number (confidence interval 95%)				
Complete Response	8.7 (1.1 to 28)	0 (-99999 to 99999)		
Partial Response	56.5 (34.5 to 76.8)	50 (6.8 to 93.2)		
Stable Disease	13 (2.8 to 33.6)	50 (6.8 to 93.2)		
Progressive Disease	21.7 (7.5 to 43.7)	0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response is defined as time interval from the time that measurement criteria are first met for CR/PR (whichever is first recorded) until first date that progressive disease is objectively documented or death due to any cause. Participants who did not progress nor die were censored at last valid response assessment. FAS. Participants who were responders among those who were had anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here 'n' is participants analysed for each category. Duration of response was calculated by Kaplan-Meier estimation. Here 99999 indicates that Median/Upper/lower limits of CI were not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (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	1	13	5	25
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,10,3,20,15,2)	1.9 (-99999 to 99999)	8.3 (1.1 to 11.2)	4 (3.7 to 99999)	14.8 (7.4 to 99999)

Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (5.6 to 99999)

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	23	4		
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,10,3,20,15,2)	9.9 (3.6 to 99999)	29.7 (-99999 to 99999)		
Without Prior Treatment with Crzb (n=0,1,1,3,2,1)	99999 (9.2 to 99999)	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)

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 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). PFS was calculated by Kaplan-Meier estimation. Full analysis set. Participants with anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here 'n' is participants analysed for each category. Here 99999 indicates that Median/Upper/lower limits of CI were not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (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	1	13	5	25
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,9,4,13,14,3)	3.5 (-99999 to 99999)	11.9 (3.5 to 18.7)	5.7 (0.5 to 99999)	16.3 (9.2 to 99999)
Without Prior Treatment with Crzb (n=0,0,0,1,1,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (7.4 to 99999)

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	23	4		
Units: months				
median (confidence interval 95%)				
With Prior Treatment with Crzb (n=1,9,4,13,14,3)	10.8 (4.5 to 99999)	7.3 (1.9 to 31.5)		
Without Prior Treatment with Crzb (n=0,0,0,1,1,0)	99999 (11.1 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

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. Full analysis set. Participants with anaplastic lymphoma kinase (ALK) and non-small cell lung cancer (NSCLC) were evaluated for this outcome measure. Here, 99999 indicates that median overall survival 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 up to data cut-off date: 16 November 2015 (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	1	14	6	28
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	9.9999 (8 to 18.7)	99999 (-99999 to 99999)	9.9999 (1.4 to 22.5)

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%)	9.9999 (0.2 to 17.6)	9.9999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intracranial Response

End point title	Duration of Intracranial Response

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 only non-measurable brain metastases at baseline were evaluated for this outcome measure. Here 99999 indicates that median/upper/lower limits of CI were not reached due to low number of participants with events.

End point type	Secondary

End point timeframe:

Screening and at 8-week intervals thereafter up to data cut-off date: 16 November 2015 (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[4]	8	1	18
Units: months				
median (confidence interval 95%)	(to)	12.9 (-99999 to 99999)	5 (-99999 to 99999)	11.4 (7.5 to 11.4)

Notes:

[4] - 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

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: ng/mL				
arithmetic mean (standard deviation)	249.5 (± 99999)	491.67 (± 223.95)	634.07 (± 310.05)	942.3 (± 472.33)

End point values	Brigatinib 180 mg	Brigatinib 240 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	7		
Units: ng/mL				
arithmetic mean (standard deviation)	1694.3 (± 1014.3)	1694.3 (± 1014.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib

End point description:

Analysis was performed on all enrolled participants in the study who received at least one dose of brigatinib. Here, 99999 indicates that standard deviation was not calculated.

End point type	Secondary

End point timeframe:

Cycle 2 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: hour				
arithmetic mean (standard deviation)	2.49 (± 99999)	1.1 (± 0.656)	2.56 (± 1.98)	2.79 (± 1.88)

End point values	Brigatinib 180 mg	Brigatinib 240 mg		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	7		
Units: hour				
arithmetic mean (standard deviation)	2.66 (± 1.46)	2.44 (± 1.13)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Any adverse event reported on or after the day of first dose of study drug (approximately up to 50 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	AP26113 30 mg QD/60 mg QD

Reporting group description:

AP26113 30 mg/60 mg (lower doses than RP2Ds), tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Reporting group title	AP26113 90 mg QD

Reporting group description:

AP26113 90 mg (lower dose than RP2Ds), tablets, orally, once daily (QD) in each cycle of 28 days (approximately, up to 44.4 months).

Reporting group title	AP26113 120 mg QD/60 mg BID

Reporting group description:

AP26113 120 mg, once daily or 60 mg, twice daily (BID) (doses between the two RP2Ds), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

Reporting group title	AP26113 90 mg QD-180 mg QD

Reporting group description:

AP26113 90 mg, tablets, orally, once daily for up to 7 days followed by 180 mg (higher RP2D), tablets, orally, once daily in each cycle of 28 days (approximately, up to 44.4 months).

Reporting group title	AP26113 180 mg QD/90 mg BID

Reporting group description:

AP26113 180 mg, once daily or 90 mg, twice daily (BID), tablets, orally in each cycle of 28 days (approximately, up to 44.4 months).

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

Reporting group description:

AP26113 240 mg, once daily (QD) or 120 mg, twice daily (BID) or 300 mg once daily (doses higher than 180 mg QD), tablets, orally, in each cycle of 28 days (approximately, up to 44.4 months).

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%)	9 / 18 (50.00%)	10 / 18 (55.56%)
number of deaths (all causes)	0	3	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	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
Metastatic 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
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
Asthenia			
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
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
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			
Dyspnoea			
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
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	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%)	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
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
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

Computerised tomogram thorax abnormal			
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
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
Left ventricular dysfunction			
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
Nervous system disorders			
Seizure			
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
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%)	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
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			

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			

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
Lower respiratory tract infection bacterial			
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
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
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

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	9 / 32 (28.13%)	25 / 48 (52.08%)	10 / 15 (66.67%)
number of deaths (all causes)	3	8	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
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 / 4	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	3 / 32 (9.38%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	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%)	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
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
Metastatic 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
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%)	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

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
Asthenia			
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
Chest pain			
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
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			
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	4 / 15 (26.67%)
occurrences causally related to treatment / all	0 / 2	3 / 3	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Hypoxia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	1 / 1	2 / 2	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%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	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%)	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
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
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%)	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
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
Computerised tomogram thorax abnormal			
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	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 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
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 / 4	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%)	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
Left ventricular dysfunction			
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
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
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
Embolic 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%)	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
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%)	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
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
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
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			
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%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	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
Lower respiratory tract infection bacterial			
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
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			

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

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%)	18 / 18 (100.00%)	18 / 18 (100.00%)
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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	5 / 18 (27.78%)
occurrences (all)	0	1	6
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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	9 / 18 (50.00%)	6 / 18 (33.33%)
occurrences (all)	2	14	7
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	3 / 18 (16.67%)
occurrences (all)	1	1	3
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%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	3
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	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
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	6 / 18 (33.33%)	6 / 18 (33.33%)
occurrences (all)	1	7	10
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	5 / 18 (27.78%)
occurrences (all)	0	3	6
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	2	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%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
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	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	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%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	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	1
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	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	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%)	4 / 18 (22.22%)	5 / 18 (27.78%)
occurrences (all)	0	10	12
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	4 / 18 (22.22%)
occurrences (all)	0	6	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	6 / 18 (33.33%)
occurrences (all)	0	4	8
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	3 / 18 (16.67%)
occurrences (all)	0	4	3
Blood insulin increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	4	5
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	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	3
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	0	0
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%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	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%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	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			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
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
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Palpitations			

subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
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	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	7 / 18 (38.89%)	7 / 18 (38.89%)
occurrences (all)	0	12	8
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	0	7	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	3
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Amnesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Visual field defect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	5
Increased tendency to bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	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	3	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%)	1 / 18 (5.56%)	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
Colour blindness acquired			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	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	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	6 / 18 (33.33%)	8 / 18 (44.44%)
occurrences (all)	3	7	9

Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	7 / 18 (38.89%)	7 / 18 (38.89%)
occurrences (all)	1	11	10
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	6 / 18 (33.33%)	5 / 18 (27.78%)
occurrences (all)	1	6	8
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	5 / 18 (27.78%)
occurrences (all)	2	2	6
Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	2 / 18 (11.11%)	3 / 18 (16.67%)
occurrences (all)	3	2	3
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	1 / 18 (5.56%)
occurrences (all)	0	3	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%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Sensitivity of teeth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	2 / 18 (11.11%)
occurrences (all)	0	1	3
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

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 6 (0.00%)	3 / 18 (16.67%)	2 / 18 (11.11%)
occurrences (all)	0	4	2
Photosensitivity reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	7
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%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Onychoclasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	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	3	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	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
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
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
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	1 / 18 (5.56%)	3 / 18 (16.67%)
occurrences (all)	1	8	3
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	5 / 18 (27.78%)
occurrences (all)	1	0	6
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	1	5	0
Pain in extremity			

subjects affected / exposed	1 / 6 (16.67%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	1	5	3
Musculoskeletal chest pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
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%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	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%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
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
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	3 / 18 (16.67%)
occurrences (all)	0	1	3
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	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%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	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%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	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	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Diarrhoea infectious			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Infectious pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Laryngitis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nail infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nasal herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

Otitis externa			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	5 / 18 (27.78%)	1 / 18 (5.56%)
occurrences (all)	0	5	1
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	6
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%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	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%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Increased appetite			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 32 (40.63%)	16 / 48 (33.33%)	12 / 15 (80.00%)
occurrences (all)	16	25	15
Oedema peripheral			
subjects affected / exposed	6 / 32 (18.75%)	3 / 48 (6.25%)	5 / 15 (33.33%)
occurrences (all)	6	5	6
Pyrexia			
subjects affected / exposed	5 / 32 (15.63%)	6 / 48 (12.50%)	2 / 15 (13.33%)
occurrences (all)	5	7	2
Pain			
subjects affected / exposed	3 / 32 (9.38%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Chest discomfort			
subjects affected / exposed	3 / 32 (9.38%)	5 / 48 (10.42%)	2 / 15 (13.33%)
occurrences (all)	3	6	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	3 / 32 (9.38%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	5	3	1
Asthenia			
subjects affected / exposed	1 / 32 (3.13%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	1	6	1
Chills			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	1	1	5
Gait disturbance			
subjects affected / exposed	2 / 32 (6.25%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	2	3	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%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	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%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			
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	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nipple pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	11 / 32 (34.38%)	13 / 48 (27.08%)	8 / 15 (53.33%)
occurrences (all)	17	17	10
Dyspnoea			
subjects affected / exposed	7 / 32 (21.88%)	7 / 48 (14.58%)	3 / 15 (20.00%)
occurrences (all)	8	9	4
Dyspnoea exertional			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	4	2
Oropharyngeal pain			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	2	4	1
Epistaxis			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	2 / 15 (13.33%)
occurrences (all)	1	4	2
Productive cough			
subjects affected / exposed	3 / 32 (9.38%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	3	3	0
Nasal congestion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Haemoptysis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	3	3	2
Hypoxia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	1	2	3
Rhinorrhoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Sinus congestion			
subjects affected / exposed	3 / 32 (9.38%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Dysphonia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	2	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	1	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%)	3 / 48 (6.25%)	3 / 15 (20.00%)
occurrences (all)	6	3	3
Anxiety			
subjects affected / exposed	4 / 32 (12.50%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	4	1	1
Depression			
subjects affected / exposed	3 / 32 (9.38%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	3	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	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
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	9 / 32 (28.13%)	8 / 48 (16.67%)	3 / 15 (20.00%)
occurrences (all)	22	14	6
Lipase increased			
subjects affected / exposed	10 / 32 (31.25%)	6 / 48 (12.50%)	2 / 15 (13.33%)
occurrences (all)	21	24	5
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 32 (21.88%)	7 / 48 (14.58%)	2 / 15 (13.33%)
occurrences (all)	10	12	4
Alanine aminotransferase increased			
subjects affected / exposed	4 / 32 (12.50%)	4 / 48 (8.33%)	1 / 15 (6.67%)
occurrences (all)	10	4	4
Blood insulin increased			
subjects affected / exposed	3 / 32 (9.38%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	5	9	0
Weight decreased			
subjects affected / exposed	3 / 32 (9.38%)	3 / 48 (6.25%)	2 / 15 (13.33%)
occurrences (all)	3	4	3
Blood creatinine increased			
subjects affected / exposed	3 / 32 (9.38%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Lymphocyte count decreased			
subjects affected / exposed	3 / 32 (9.38%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	4	2	1
Weight increased			
subjects affected / exposed	0 / 32 (0.00%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	0	4	1
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Blood testosterone decreased			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	0	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%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
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%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	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			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
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
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	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
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%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			

subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	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	12 / 32 (37.50%)	14 / 48 (29.17%)	6 / 15 (40.00%)
occurrences (all)	13	18	8
Dizziness			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	4	3	1
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 32 (15.63%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	5	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	4	2
Tremor			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Amnesia			
subjects affected / exposed	1 / 32 (3.13%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	5	0
Balance disorder			
subjects affected / exposed	0 / 32 (0.00%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	3	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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 32 (12.50%)	2 / 48 (4.17%)	3 / 15 (20.00%)
occurrences (all)	6	4	4
Increased tendency to bruise			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Leukocytosis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Deafness unilateral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	4 / 32 (12.50%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	4	4	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%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	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%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	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	1 / 32 (3.13%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	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
Colour blindness acquired			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	14 / 32 (43.75%)	31 / 48 (64.58%)	8 / 15 (53.33%)
occurrences (all)	15	42	11
Diarrhoea			
subjects affected / exposed	15 / 32 (46.88%)	18 / 48 (37.50%)	8 / 15 (53.33%)
occurrences (all)	17	32	28

Constipation			
subjects affected / exposed	9 / 32 (28.13%)	7 / 48 (14.58%)	5 / 15 (33.33%)
occurrences (all)	10	7	5
Vomiting			
subjects affected / exposed	5 / 32 (15.63%)	15 / 48 (31.25%)	5 / 15 (33.33%)
occurrences (all)	8	24	5
Abdominal pain			
subjects affected / exposed	7 / 32 (21.88%)	9 / 48 (18.75%)	2 / 15 (13.33%)
occurrences (all)	8	12	5
Dry mouth			
subjects affected / exposed	4 / 32 (12.50%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	4	1	2
Abdominal distension			
subjects affected / exposed	1 / 32 (3.13%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	1	4	0
Abdominal discomfort			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	2	4	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 32 (3.13%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Dyspepsia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Dysphagia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	0	2	4
Aphthous stomatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Sensitivity of teeth			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	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%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	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	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	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	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	4 / 32 (12.50%)	7 / 48 (14.58%)	1 / 15 (6.67%)
occurrences (all)	6	12	1
Photosensitivity reaction			
subjects affected / exposed	3 / 32 (9.38%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	4	6	0
Pruritus			
subjects affected / exposed	6 / 32 (18.75%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	6	3	0
Dry skin			
subjects affected / exposed	4 / 32 (12.50%)	3 / 48 (6.25%)	0 / 15 (0.00%)
occurrences (all)	5	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%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	0	3	1
Hyperhidrosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	1	1	2
Onychoclasis			
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	2 / 32 (6.25%)	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%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	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	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	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%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nail growth abnormal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	0 / 15 (0.00%)
occurrences (all)	2	4	0

Proteinuria			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Haematuria			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Dysuria			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Renal failure			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 32 (6.25%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 32 (21.88%)	11 / 48 (22.92%)	3 / 15 (20.00%)
occurrences (all)	9	16	6
Back pain			
subjects affected / exposed	7 / 32 (21.88%)	7 / 48 (14.58%)	1 / 15 (6.67%)
occurrences (all)	7	8	1
Musculoskeletal pain			
subjects affected / exposed	2 / 32 (6.25%)	4 / 48 (8.33%)	3 / 15 (20.00%)
occurrences (all)	2	5	3
Arthralgia			
subjects affected / exposed	10 / 32 (31.25%)	6 / 48 (12.50%)	0 / 15 (0.00%)
occurrences (all)	15	9	0
Pain in extremity			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	2 / 15 (13.33%)
occurrences (all)	3	3	3
Musculoskeletal chest pain			

subjects affected / exposed	3 / 32 (9.38%)	3 / 48 (6.25%)	1 / 15 (6.67%)
occurrences (all)	4	3	1
Joint swelling			
subjects affected / exposed	5 / 32 (15.63%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	5	2	0
Myalgia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Bone pain			
subjects affected / exposed	0 / 32 (0.00%)	5 / 48 (10.42%)	0 / 15 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal discomfort			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Flank pain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pain in jaw			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Arthritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	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	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Osteopenia			
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	7 / 32 (21.88%)	5 / 48 (10.42%)	3 / 15 (20.00%)
occurrences (all)	8	5	3
Nasopharyngitis			
subjects affected / exposed	4 / 32 (12.50%)	5 / 48 (10.42%)	1 / 15 (6.67%)
occurrences (all)	5	6	1
Urinary tract infection			
subjects affected / exposed	3 / 32 (9.38%)	6 / 48 (12.50%)	1 / 15 (6.67%)
occurrences (all)	4	9	1
Sinusitis			
subjects affected / exposed	4 / 32 (12.50%)	1 / 48 (2.08%)	4 / 15 (26.67%)
occurrences (all)	6	1	5
Pneumonia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Bronchitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 48 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Influenza			
subjects affected / exposed	1 / 32 (3.13%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Viral infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 48 (2.08%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis viral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Diarrhoea infectious			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Folliculitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Fungal skin infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	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
Lung infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
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	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 32 (25.00%)	9 / 48 (18.75%)	5 / 15 (33.33%)
occurrences (all)	8	9	5
Hypophosphataemia			
subjects affected / exposed	6 / 32 (18.75%)	3 / 48 (6.25%)	2 / 15 (13.33%)
occurrences (all)	8	3	3
Hypomagnesaemia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 48 (4.17%)	4 / 15 (26.67%)
occurrences (all)	2	2	4
Hypokalaemia			
subjects affected / exposed	3 / 32 (9.38%)	2 / 48 (4.17%)	3 / 15 (20.00%)
occurrences (all)	3	2	3
Hyponatraemia			
subjects affected / exposed	3 / 32 (9.38%)	1 / 48 (2.08%)	1 / 15 (6.67%)
occurrences (all)	4	1	2
Dehydration			
subjects affected / exposed	0 / 32 (0.00%)	2 / 48 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	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			

subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 48 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

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