



Clinical trial results:

A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib Summary

EudraCT number	2013-002134-21
Trial protocol	DE ES IT NL DK AT BE SE NO
Global end of trial date	27 February 2020

Results information

Result version number	v2 (current)
This version publication date	13 March 2021
First version publication date	29 June 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	AP26113-13-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094573
WHO universal trial number (UTN)	U1111-1196-8246

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy and safety of two different dosing regimens of brigatinib (AP26113) in participants with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on therapy with crizotinib.

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	04 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Korea, Republic of: 46
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 46

Worldwide total number of subjects	222
EEA total number of subjects	101

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)	170
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 71 investigative sites in the United States, Canada, Europe, Australia, and Asia from 04 Jun 2014 to 27 February 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) who had progressed on crizotinib were enrolled to receive brigatinib 90 mg, once daily or brigatinib 90-180 mg, once daily.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brigatinib 90 mg

Arm description:

Brigatinib 90 mg, tablets, orally, once daily in each Cycle of 28 days until disease progression or intolerable toxicity (median duration of exposure was 402 days).

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

Dosage and administration details:

AP26113 tablets and capsules.

Arm title	Brigatinib 90 mg - 180 mg
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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 until disease progression or intolerable toxicity (median duration of exposure was 522 days).

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

Dosage and administration details:

AP26113 tablets and capsules.

Number of subjects in period 1	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg
Started	112	110
Treated	109	110
Completed	0	0
Not completed	112	110
Adverse event, serious fatal	11	3
Physician decision	4	4
Clinical Progressive Disease	9	13
Documented Progressive Disease (RECIST 1.1)	63	50
Adverse event, non-fatal	4	14
Subject Received a New Systemic Anticancer Therapy	1	-
Non-compliance with study drug	1	1
Withdrawal by Subject	6	8
Randomized but not Treated	3	-
Site Terminated by Sponsor	10	17

Baseline characteristics

Reporting groups

Reporting group title	Brigatinib 90 mg
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Reporting group description:

Brigatinib 90 mg, tablets, orally, once daily in each Cycle of 28 days until disease progression or intolerable toxicity (median duration of exposure was 402 days).

Reporting group title	Brigatinib 90 mg - 180 mg
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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 until disease progression or intolerable toxicity (median duration of exposure was 522 days).

Reporting group values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg	Total
Number of subjects	112	110	222
Age Categorical Units: Subjects			
18-49 years	50	33	83
50-64 years	40	47	87
65-74 years	20	23	43
≥75 years	2	7	9
Age Continuous Units: years			
arithmetic mean	51.5	55.4	
standard deviation	± 13.03	± 12.98	-
Gender, Male/Female Units: Subjects			
Female	62	64	126
Male	50	46	96
Race/Ethnicity, Customized Units: Subjects			
White	72	76	148
Black or African American	1	2	3
Asian	39	30	69
Unknown	0	2	2
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	5	8	13
Not Hispanic or Latino	107	102	209
Region of Enrollment Units: Subjects			
Australia	3	6	9
Austria	3	6	9
Belgium	3	2	5
Canada	2	1	3
Denmark	2	6	8
France	4	2	6
Germany	7	7	14
Hong Kong	6	0	6

Italy	15	14	29
Netherlands	6	6	12
Norway	1	1	2
Singapore	4	3	7
Spain	5	7	12
Sweden	2	2	4
Switzerland	0	1	1
United Kingdom	2	1	3
United States	21	25	46
Korea, Republic Of	26	20	46

End points

End points reporting groups

Reporting group title	Brigatinib 90 mg
Reporting group description: Brigatinib 90 mg, tablets, orally, once daily in each Cycle of 28 days until disease progression or intolerable toxicity (median duration of exposure was 402 days).	
Reporting group title	Brigatinib 90 mg - 180 mg
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 until disease progression or intolerable toxicity (median duration of exposure was 522 days).	

Primary: Confirmed Objective Response Rate (ORR) as Assessed by Investigator

End point title	Confirmed Objective Response Rate (ORR) as Assessed by Investigator ^[1]
End point description: ORR assessed by investigator, defined as percentage of participants with confirmed complete response(CR)or partial response(PR)as per response evaluation criteria in solid tumors (RECIST)v1.1(confirmed ≥4 weeks after initial response),after initiation of study treatment.CR(target lesion):Disappearance of all extranodal lesions,all pathological lymph nodes must have decreased to<10mm in short axis.CR(non-target lesion):Disappearance of all extranodal lesions, all lymph nodes must be non-pathological in size(<10mm short axis),normalization of tumor marker level.PR:≥30% decrease in sum of longest diameters(SLD)of target lesions,with baseline sum diameters as reference.Exact 2-sided 97.5% confidence interval was calculated.Treatment regimen was considered to have achieved primary objective when lower bound of 97.5% confidence interval is >20%.ITT Population:all participants who were randomized to each regimen regardless of whether they received study drug or adhered to assigned dose.	
End point type	Primary
End point timeframe: Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or up to end of the study (approximately up to 69 months)	
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: Not applicable	

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: percentage of participants				
number (confidence interval 97.5%)	45.5 (34.8 to 56.5)	57.3 (46.1 to 67.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Objective Response Rate (ORR) as Assessed by Independent

Review Committee (IRC)

End point title	Confirmed Objective Response Rate (ORR) as Assessed by Independent Review Committee (IRC)
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End point description:

ORR assessed by the IRC, was defined as the percentage of the participants with CR or PR according to RECIST v1.1 (confirmed ≥ 4 weeks after initial response), 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 (<10 mm short axis) and normalization of tumor marker level. PR: at least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters. The exact 2-sided 95% confidence interval was calculated. ITT Population: all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose.

End point type	Secondary
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End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or up to end of the study (approximately up to 69 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: percentage of participants				
number (confidence interval 95%)	51.8 (42.1 to 61.3)	56.4 (46.6 to 65.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Intracranial Central Nervous System Objective Response Rate (CNS ORR) in Participants with Measurable Active Brain Metastases

End point title	Confirmed Intracranial Central Nervous System Objective Response Rate (CNS ORR) in Participants with Measurable Active Brain Metastases
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End point description:

Confirmed intracranial CNS ORR was defined as percentage of participants with CR or PR in intracranial CNS per modification of RECIST v1.1 as evaluated by IRC after initiation of study drug. Confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial response. CR for target lesion: disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (<10 mm short axis). CR for non-target lesion: disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (<10 mm short axis) and normalization of tumor marker level. PR: at least a 30% decrease in the SLD of target lesions, with Baseline sum diameters as reference. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to assigned dose. Participants with measurable active brain metastases at Baseline were evaluated for this outcome measure.

End point type	Secondary
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End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or approximately up to 29 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	15		
Units: percentage of participants				
number (confidence interval 95%)				
CNS ORR	47.4 (24.4 to 71.1)	73.3 (44.9 to 92.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Intracranial Central Nervous System Objective Response Rate (CNS ORR) in Participants with Only Non-measurable Active Brain Metastases

End point title	Confirmed Intracranial Central Nervous System Objective Response Rate (CNS ORR) in Participants with Only Non-measurable Active Brain Metastases
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End point description:

Confirmed intracranial CNS ORR is defined as percentage of participants with CR or PR in intracranial CNS per modification of RECIST v1.1 as evaluated by IRC after initiation of study drug. Confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial response. CR for target lesion: disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (<10mm 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 SLD of target lesions, taking as reference Baseline sum diameters. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. Participants with only non-measurable active brain metastases at Baseline were evaluated for this outcome measure.

End point type	Secondary
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End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or approximately up to 29 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	36		
Units: percentage of participants				
number (confidence interval 95%)	12.1 (3.4 to 28.2)	16.7 (6.4 to 32.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial CNS Progression Free Survival (PFS) in Participants with Active Brain Metastases

End point title	Intracranial CNS Progression Free Survival (PFS) in Participants with Active Brain Metastases
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End point description:

Intracranial CNS PFS as evaluated by IRC is defined as the time interval from the date of the first dose of the study drug until the first date at which intracranial CNS disease progression, an increase of 20% or more in the sum of diameters of intracranial CNS target lesions, unequivocal progression of non-target lesions, or the appearance of new lesions in the intracranial CNS, was objectively documented by a scan, or death due to any cause, whichever occurred first. The analysis was based on the Kaplan-Meier (KM) Estimates. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. Participants with active brain metastases whether it was measurable or non-measurable at baseline were evaluated for this outcome measure.

End point type	Secondary
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End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or approximately up to 29 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: months				
median (confidence interval 95%)	12.8 (9.0 to 18.4)	12.8 (9.1 to 21.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response
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End point description:

Time to response was defined as the time interval from the date of the first dose of the study drug until the initial observation of CR or PR for participants with confirmed CR/PR. 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 SLD of target lesions, taking as reference the Baseline sum diameters. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. Participants who had confirmed CR or PR were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Up to approximately 69 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	63		
Units: months				
median (full range (min-max))	1.8 (1.7 to 11.1)	1.9 (1.0 to 35.0)		

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 was defined as time interval from 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. Patients without progressive disease or death were censored at last valid response assessment. CR (target lesion): Disappearance of all extranodal lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. CR (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: ≥30% decrease in SLD of target lesions, taking as reference the baseline sum diameters. The analysis was based on Kaplan-Meier (KM) Estimates. ITT Population: participants who were randomized to each regimen regardless of whether they received study drug or adhered to assigned dose. Participants who had confirmed CR or PR were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe:	
Up to approximately 69 months	

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	63		
Units: months				
median (confidence interval 95%)	12.0 (9.2 to 19.4)	13.8 (10.8 to 17.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time on Treatment

End point title	Time on Treatment
End point description:	
Time on treatment was defined as the time from the first to the last dose of study drug. For participants who have not discontinued, time on treatment was censored as of the last dose of the study drug. Safety Population included all participants who received at least one dose of study drug.	
End point type	Secondary

End point timeframe:
Up to approximately 69 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: days				
median (full range (min-max))	402.0 (1 to 1882)	522.0 (2 to 2030)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description: DCR was defined as percentage of randomized participants who were confirmed to have achieved CR or PR or have a best overall response as stable disease (SD) for 6 weeks or more after initiation of study drug. 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 SLD of target lesions, taking as reference baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). PD was defined as at least a 20% increase in sum of diameters of target lesions. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to assigned dose.	
End point type	Secondary
End point timeframe: Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered Cycle of 28-days) through 15 Cycles and every 3 Cycles thereafter until disease progression or up to end of the study (approximately up to 69 months)	

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: percentage of participants				
number (confidence interval 95%)	81.3 (72.8 to 88.0)	86.4 (78.5 to 92.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

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

PFS was 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). The analysis was based on the Kaplan-Meier (KM) Estimates. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose.

End point type	Secondary
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End point timeframe:

Up to approximately 69 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: months				
median (confidence interval 95%)	9.2 (7.4 to 11.1)	15.6 (11.1 to 18.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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

OS is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. Intracranial OS was calculated by Kaplan-Meier estimation. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose.9999999 = Upper limit of 95% confidence interval was not estimable due to low number of participants with event.

End point type	Secondary
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End point timeframe:

Up to approximately 69 months

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: months				
median (confidence interval 95%)				
Overall Survival	25.9 (18.2 to 45.8)	40.6 (32.5 to 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE)
End point description: An Adverse Event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE was defined as an adverse event with an onset that occurs after receiving study drug. Safety Population included all participants who received at least one dose of study drug.	
End point type	Secondary
End point timeframe: From first dose of study drug up to 30 days following the last dose of study drug (approximately up to 69 months)	

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	110		
Units: participants	109	110		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Brigatinib Plasma Concentration

End point title	Pre-dose Brigatinib Plasma Concentration
End point description: ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. Here, number of participants analyzed is the participants who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Day 1 Cycles 2, 3, 4 and 5 (each Cycle of 28-days) pre-dose	

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: ng/ml				
arithmetic mean (standard deviation)				
Cycle 2 (n=101, 97)	295.2 (± 252.0)	520.0 (± 321.9)		
Cycle 3 (n=91, 92)	263.9 (± 238.9)	537.0 (± 360.3)		
Cycle 4 (n=80, 87)	236.1 (± 188.0)	564.7 (± 415.0)		
Cycle 5 (n=80, 79)	256.4 (± 282.3)	579.7 (± 396.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported Symptoms Global Health Status/Quality of Life (QoL) Scores

End point title	Patient-reported Symptoms Global Health Status/Quality of Life (QoL) Scores
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End point description:

Patient-reported symptoms global health status/quality of life (QoL) scores based on questions 29 and 30 of European Organisation for Research and Treatment of Cancer(EORTC)QLQ-C30.First 28 questions used 4-point scale(1=not at all to 4=very much)for evaluating 5 functional scales (physical,role,cognitive,emotional,social functioning);3 symptom scales(fatigue,pain,and nausea/vomiting);last 2 questions coded on 7-point scale(1=very poor to 7=excellent).Also included Six single-item scales(dyspnea,insomnia,appetite loss,constipation,diarrhea,financial difficulties).Raw scores were linearly transformed to obtain score 0-100,where higher score represents better level of functioning.9999=Standard deviation(SD)was not evaluable for 1 participant.99999 =No participant was analyzed for time point.ITT Population:all participants randomized to each regimen regardless of whether they received study drug or adhered to assigned dose.'n'=number of participants evaluable at specific time point.

End point type	Secondary
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End point timeframe:

Baseline and at each 28-day cycle up to end of the study (up to approximately 69 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Baseline (n=108, 108)	52.39 (± 27.42)	58.49 (± 23.40)		
Cycle 2 (n=101, 97)	64.19 (± 20.73)	65.72 (± 19.54)		
Cycle 3 (n=91, 91)	65.57 (± 24.06)	68.50 (± 20.52)		
Cycle 4 (n=84, 89)	69.44 (± 20.59)	66.95 (± 20.89)		

Cycle 5 (n=82, 85)	70.12 (± 20.28)	71.86 (± 17.63)		
Cycle 6 (n=79, 82)	70.15 (± 20.18)	71.24 (± 18.66)		
Cycle 7 (n=77, 80)	67.42 (± 20.29)	70.21 (± 21.66)		
Cycle 8 (n=73, 78)	67.24 (± 22.79)	69.87 (± 20.42)		
Cycle 9 (n=70, 75)	68.45 (± 22.61)	68.67 (± 21.35)		
Cycle 10 (n=65, 70)	71.79 (± 20.61)	67.98 (± 23.25)		
Cycle 11 (n=61, 70)	72.54 (± 19.56)	68.45 (± 21.37)		
Cycle 12 (n=61, 65)	68.03 (± 23.08)	70.51 (± 21.35)		
Cycle 13 (n=58, 64)	70.11 (± 19.93)	72.79 (± 19.20)		
Cycle 14 (n=55, 57)	69.55 (± 20.04)	70.76 (± 19.42)		
Cycle 15 (n=54, 58)	70.06 (± 21.08)	70.83 (± 20.66)		
Cycle 16 (n=50, 58)	68.17 (± 22.94)	72.27 (± 18.36)		
Cycle 17 (n=48, 61)	73.61 (± 18.78)	69.81 (± 20.36)		
Cycle 18 (n=43, 58)	67.64 (± 22.80)	71.55 (± 17.94)		
Cycle 19 (n=43, 55)	69.57 (± 23.14)	72.12 (± 20.49)		
Cycle 20 (n=40, 52)	66.04 (± 24.05)	72.76 (± 18.53)		
Cycle 21 (n=39, 50)	69.23 (± 22.87)	69.83 (± 19.04)		
Cycle 22 (n=36, 46)	72.69 (± 21.70)	71.20 (± 18.90)		
Cycle 23 (n=35, 47)	72.38 (± 21.93)	71.10 (± 20.10)		
Cycle 24 (n=32, 42)	72.66 (± 19.66)	71.43 (± 15.74)		
Cycle 25 (n=34, 39)	71.57 (± 21.72)	70.09 (± 19.38)		
Cycle 26 (n=32, 36)	71.88 (± 22.28)	69.68 (± 20.43)		
Cycle 27 (n=33, 36)	71.46 (± 20.94)	70.83 (± 21.96)		
Cycle 28 (n=31, 37)	71.24 (± 22.24)	69.59 (± 20.24)		
Cycle 29 (n=30, 37)	70.00 (± 21.73)	71.17 (± 22.27)		
Cycle 30 (n=29, 34)	69.25 (± 21.72)	70.83 (± 18.03)		
Cycle 31 (n=26, 33)	75.64 (± 17.63)	69.95 (± 18.15)		
Cycle 32 (n=25, 31)	73.00 (± 20.02)	70.97 (± 20.28)		
Cycle 33 (n=25, 32)	71.67 (± 20.41)	70.31 (± 20.84)		
Cycle 34 (n=21, 31)	72.62 (± 20.61)	69.62 (± 20.70)		
Cycle 35 (n=21, 31)	72.22 (± 18.88)	66.67 (± 22.97)		

Cycle 36 (n=20, 30)	68.33 (± 22.72)	71.67 (± 19.89)		
Cycle 37 (n=20, 30)	73.33 (± 19.42)	72.50 (± 19.47)		
Cycle 38 (n=18, 29)	68.98 (± 22.10)	72.99 (± 17.49)		
Cycle 39 (n=17, 26)	68.63 (± 25.09)	73.72 (± 19.96)		
Cycle 40 (n=17, 26)	71.57 (± 24.13)	69.87 (± 23.10)		
Cycle 41 (n=17, 26)	72.55 (± 21.20)	68.27 (± 22.98)		
Cycle 42 (n=17, 24)	72.06 (± 21.84)	72.57 (± 20.78)		
Cycle 43 (n=17, 23)	67.65 (± 24.63)	71.01 (± 22.17)		
Cycle 44 (n=17, 22)	72.55 (± 20.57)	73.48 (± 19.35)		
Cycle 45 (n=14, 22)	66.67 (± 19.88)	72.35 (± 22.03)		
Cycle 46 (n=15, 22)	70.56 (± 19.12)	71.59 (± 20.52)		
Cycle 47 (n=14, 21)	60.12 (± 25.36)	73.02 (± 19.88)		
Cycle 48 (n=13, 21)	65.38 (± 20.93)	74.60 (± 19.80)		
Cycle 49 (n=13, 20)	57.69 (± 24.88)	71.67 (± 22.69)		
Cycle 50 (n=13, 20)	61.54 (± 26.47)	70.00 (± 24.54)		
Cycle 51 (n=12, 21)	63.19 (± 23.96)	69.05 (± 22.69)		
Cycle 52 (n=12, 21)	56.94 (± 22.71)	72.22 (± 22.26)		
Cycle 53 (n=12, 20)	61.11 (± 21.42)	70.83 (± 23.02)		
Cycle 54 (n=12, 19)	61.81 (± 25.24)	71.49 (± 20.47)		
Cycle 55 (n=10, 19)	63.33 (± 26.12)	72.37 (± 20.42)		
Cycle 56 (n=9, 18)	63.89 (± 23.94)	73.61 (± 19.23)		
Cycle 57 (n=10, 17)	65.00 (± 19.95)	73.53 (± 19.37)		
Cycle 58 (n=10, 14)	65.00 (± 25.09)	70.83 (± 20.61)		
Cycle 59 (n=9, 14)	64.81 (± 25.27)	71.43 (± 19.81)		
Cycle 60 (n=8, 9)	70.83 (± 27.82)	73.15 (± 19.44)		
Cycle 61 (n=7, 8)	71.43 (± 28.41)	78.13 (± 19.89)		
Cycle 62 (n=5, 7)	66.67 (± 23.57)	79.76 (± 15.85)		
Cycle 63 (n=4, 7)	58.33 (± 31.91)	78.57 (± 17.91)		
Cycle 64 (n=3, 7)	61.11 (± 34.69)	77.38 (± 20.81)		
Cycle 65 (n=2, 6)	75.00 (± 35.36)	76.39 (± 22.62)		
Cycle 66 (n=2, 4)	75.00 (± 35.36)	77.08 (± 31.46)		

Cycle 67 (n=2, 1)	75.00 (± 35.36)	41.67 (± 9999)		
Cycle 68 (n=0, 1)	99999 (± 99999)	41.67 (± 9999)		
Cycle 69 (n=0, 1)	99999 (± 99999)	58.33 (± 9999)		
Cycle 70 (n=0, 1)	99999 (± 99999)	41.67 (± 9999)		
Cycle 71 (n=0, 1)	99999 (± 99999)	41.67 (± 9999)		
Cycle 72 (n=0, 1)	99999 (± 99999)	75.00 (± 9999)		
End of Treatment (n=80, 68)	52.29 (± 28.25)	61.15 (± 23.15)		
Follow-Up 30 Days After Last Dose (n=43, 45)	61.05 (± 30.58)	61.67 (± 23.33)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days following the last dose of study drug (approximately up to 69 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	AP26113 90 mg - 180 mg
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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 until disease progression or intolerable toxicity (median duration of exposure was 522 days).

Reporting group title	AP26113 90 mg
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Reporting group description:

Brigatinib 90 mg, tablets, orally, once daily in each Cycle of 28 days until disease progression or intolerable toxicity (median duration of exposure was 402 days).

Serious adverse events	AP26113 90 mg - 180 mg	AP26113 90 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 110 (62.73%)	58 / 109 (53.21%)	
number of deaths (all causes)	14	22	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm Progression			
subjects affected / exposed	8 / 110 (7.27%)	15 / 109 (13.76%)	
occurrences causally related to treatment / all	0 / 8	0 / 15	
deaths causally related to treatment / all	0 / 7	0 / 9	
Malignant Pleural Effusion			
subjects affected / exposed	4 / 110 (3.64%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases To Central Nervous System			

subjects affected / exposed	3 / 110 (2.73%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases To Meninges			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowens Disease			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Liver			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases To Peritoneum			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Malignant Melanoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Cancer			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Associated Fever			

subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Behcets Syndrome			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac Artery Stenosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General Physical Health Deterioration			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Site Thrombosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Euthanasia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	10 / 110 (9.09%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	11 / 11	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 110 (4.55%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary Embolism			
subjects affected / exposed	2 / 110 (1.82%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea Exertional			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	2 / 110 (1.82%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory Failure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophagobronchial Fistula			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	2 / 110 (1.82%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Occlusion			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Necrosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Pneumonitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Laceration			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 110 (0.91%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous System Disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure			
subjects affected / exposed	1 / 110 (0.91%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple Partial Seizures			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 110 (1.82%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive Disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperaesthesia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Pressure Increased			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraesthesia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic Clonic Movements			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph Node Pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 110 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Macular Oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food Poisoning			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	0 / 110 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth Socket Haemorrhage			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis Acute			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice Cholestatic			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			
subjects affected / exposed	2 / 110 (1.82%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Allergic			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic Dermatomyositis			

subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Erythematous			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain In Extremity			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Necrosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	13 / 110 (11.82%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	1 / 13	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Appendicitis			
subjects affected / exposed	2 / 110 (1.82%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 110 (0.91%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Bacterial			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tuberculous Pleurisy			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Urinary Tract Infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma Infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 110 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased Appetite			

subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AP26113 90 mg - 180 mg	AP26113 90 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 110 (95.45%)	108 / 109 (99.08%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	35 / 110 (31.82%)	21 / 109 (19.27%)	
occurrences (all)	49	27	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	41 / 110 (37.27%)	34 / 109 (31.19%)	
occurrences (all)	53	40	
Pyrexia			
subjects affected / exposed	11 / 110 (10.00%)	23 / 109 (21.10%)	
occurrences (all)	14	48	
Asthenia			
subjects affected / exposed	19 / 110 (17.27%)	16 / 109 (14.68%)	
occurrences (all)	27	20	
Oedema Peripheral			
subjects affected / exposed	14 / 110 (12.73%)	13 / 109 (11.93%)	
occurrences (all)	14	23	
Non-Cardiac Chest Pain			
subjects affected / exposed	5 / 110 (4.55%)	6 / 109 (5.50%)	
occurrences (all)	7	9	
Influenza Like Illness			

subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 11	8 / 109 (7.34%) 9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 110 (40.91%)	35 / 109 (32.11%)	
occurrences (all)	67	54	
Dyspnoea			
subjects affected / exposed	31 / 110 (28.18%)	28 / 109 (25.69%)	
occurrences (all)	40	37	
Oropharyngeal Pain			
subjects affected / exposed	11 / 110 (10.00%)	12 / 109 (11.01%)	
occurrences (all)	12	17	
Dysphonia			
subjects affected / exposed	7 / 110 (6.36%)	8 / 109 (7.34%)	
occurrences (all)	7	20	
Productive Cough			
subjects affected / exposed	9 / 110 (8.18%)	10 / 109 (9.17%)	
occurrences (all)	11	10	
Haemoptysis			
subjects affected / exposed	8 / 110 (7.27%)	4 / 109 (3.67%)	
occurrences (all)	9	4	
Dyspnoea Exertional			
subjects affected / exposed	2 / 110 (1.82%)	6 / 109 (5.50%)	
occurrences (all)	2	7	
Epistaxis			
subjects affected / exposed	8 / 110 (7.27%)	4 / 109 (3.67%)	
occurrences (all)	10	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 110 (13.64%)	20 / 109 (18.35%)	
occurrences (all)	16	22	
Anxiety			
subjects affected / exposed	11 / 110 (10.00%)	3 / 109 (2.75%)	
occurrences (all)	12	3	
Investigations			

Blood Creatine Phosphokinase Increased			
subjects affected / exposed	41 / 110 (37.27%)	24 / 109 (22.02%)	
occurrences (all)	73	40	
Amylase Increased			
subjects affected / exposed	20 / 110 (18.18%)	16 / 109 (14.68%)	
occurrences (all)	37	23	
Aspartate Aminotransferase Increased			
subjects affected / exposed	22 / 110 (20.00%)	15 / 109 (13.76%)	
occurrences (all)	35	22	
Lipase Increased			
subjects affected / exposed	23 / 110 (20.91%)	15 / 109 (13.76%)	
occurrences (all)	54	18	
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	10 / 110 (9.09%)	3 / 109 (2.75%)	
occurrences (all)	15	3	
Alanine Aminotransferase Increased			
subjects affected / exposed	18 / 110 (16.36%)	15 / 109 (13.76%)	
occurrences (all)	29	16	
Weight Decreased			
subjects affected / exposed	7 / 110 (6.36%)	8 / 109 (7.34%)	
occurrences (all)	7	8	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	6 / 110 (5.45%)	7 / 109 (6.42%)	
occurrences (all)	9	7	
Blood Creatinine Increased			
subjects affected / exposed	8 / 110 (7.27%)	5 / 109 (4.59%)	
occurrences (all)	11	9	
Electrocardiogram Qt Prolonged			
subjects affected / exposed	8 / 110 (7.27%)	4 / 109 (3.67%)	
occurrences (all)	13	5	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 110 (6.36%)	2 / 109 (1.83%)	
occurrences (all)	7	3	

Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 110 (5.45%)	1 / 109 (0.92%)	
occurrences (all)	8	1	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 110 (40.00%)	39 / 109 (35.78%)	
occurrences (all)	76	82	
Dizziness			
subjects affected / exposed	22 / 110 (20.00%)	18 / 109 (16.51%)	
occurrences (all)	25	24	
Paraesthesia			
subjects affected / exposed	12 / 110 (10.91%)	13 / 109 (11.93%)	
occurrences (all)	17	15	
Peripheral Sensory Neuropathy			
subjects affected / exposed	10 / 110 (9.09%)	8 / 109 (7.34%)	
occurrences (all)	12	8	
Memory Impairment			
subjects affected / exposed	11 / 110 (10.00%)	4 / 109 (3.67%)	
occurrences (all)	11	5	
Seizure			
subjects affected / exposed	11 / 110 (10.00%)	4 / 109 (3.67%)	
occurrences (all)	14	4	
Hypoaesthesia			
subjects affected / exposed	6 / 110 (5.45%)	5 / 109 (4.59%)	
occurrences (all)	6	6	
Cognitive Disorder			
subjects affected / exposed	6 / 110 (5.45%)	3 / 109 (2.75%)	
occurrences (all)	6	4	
Tremor			
subjects affected / exposed	6 / 110 (5.45%)	2 / 109 (1.83%)	
occurrences (all)	7	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 110 (7.27%)	8 / 109 (7.34%)	
occurrences (all)	11	8	
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 16	3 / 109 (2.75%) 3	
Eye disorders Vision Blurred subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 11	7 / 109 (6.42%) 8	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	55 / 110 (50.00%) 86	47 / 109 (43.12%) 82	
Diarrhoea subjects affected / exposed occurrences (all)	51 / 110 (46.36%) 163	34 / 109 (31.19%) 64	
Vomiting subjects affected / exposed occurrences (all)	39 / 110 (35.45%) 106	44 / 109 (40.37%) 83	
Constipation subjects affected / exposed occurrences (all)	28 / 110 (25.45%) 39	29 / 109 (26.61%) 36	
Abdominal Pain subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 15	13 / 109 (11.93%) 16	
Dyspepsia subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 10	8 / 109 (7.34%) 8	
Stomatitis subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 21	5 / 109 (4.59%) 5	
Dry Mouth subjects affected / exposed occurrences (all)	11 / 110 (10.00%) 12	4 / 109 (3.67%) 4	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 17	11 / 109 (10.09%) 13	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	4 / 110 (3.64%)	6 / 109 (5.50%)	
occurrences (all)	4	6	
Pruritus			
subjects affected / exposed	15 / 110 (13.64%)	12 / 109 (11.01%)	
occurrences (all)	19	13	
Dermatitis Acneiform			
subjects affected / exposed	4 / 110 (3.64%)	7 / 109 (6.42%)	
occurrences (all)	4	7	
Rash Erythematous			
subjects affected / exposed	14 / 110 (12.73%)	9 / 109 (8.26%)	
occurrences (all)	16	13	
Dry Skin			
subjects affected / exposed	3 / 110 (2.73%)	8 / 109 (7.34%)	
occurrences (all)	4	12	
Rash Maculo-Papular			
subjects affected / exposed	7 / 110 (6.36%)	3 / 109 (2.75%)	
occurrences (all)	9	4	
Rash Pruritic			
subjects affected / exposed	8 / 110 (7.27%)	2 / 109 (1.83%)	
occurrences (all)	9	3	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	9 / 110 (8.18%)	3 / 109 (2.75%)	
occurrences (all)	10	3	
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	28 / 110 (25.45%)	17 / 109 (15.60%)	
occurrences (all)	37	30	
Arthralgia			
subjects affected / exposed	21 / 110 (19.09%)	19 / 109 (17.43%)	
occurrences (all)	25	26	
Back Pain			
subjects affected / exposed	30 / 110 (27.27%)	16 / 109 (14.68%)	
occurrences (all)	35	22	
Pain in extremity			

subjects affected / exposed	15 / 110 (13.64%)	17 / 109 (15.60%)	
occurrences (all)	17	23	
Myalgia			
subjects affected / exposed	17 / 110 (15.45%)	7 / 109 (6.42%)	
occurrences (all)	24	11	
Musculoskeletal Pain			
subjects affected / exposed	15 / 110 (13.64%)	9 / 109 (8.26%)	
occurrences (all)	19	10	
Musculoskeletal Chest Pain			
subjects affected / exposed	10 / 110 (9.09%)	7 / 109 (6.42%)	
occurrences (all)	15	8	
Neck Pain			
subjects affected / exposed	13 / 110 (11.82%)	4 / 109 (3.67%)	
occurrences (all)	17	4	
Muscular Weakness			
subjects affected / exposed	4 / 110 (3.64%)	6 / 109 (5.50%)	
occurrences (all)	5	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 110 (13.64%)	15 / 109 (13.76%)	
occurrences (all)	32	25	
Upper Respiratory Tract Infection			
subjects affected / exposed	10 / 110 (9.09%)	13 / 109 (11.93%)	
occurrences (all)	13	18	
Urinary Tract Infection			
subjects affected / exposed	13 / 110 (11.82%)	9 / 109 (8.26%)	
occurrences (all)	20	17	
Pneumonia			
subjects affected / exposed	15 / 110 (13.64%)	3 / 109 (2.75%)	
occurrences (all)	16	4	
Bronchitis			
subjects affected / exposed	6 / 110 (5.45%)	5 / 109 (4.59%)	
occurrences (all)	9	6	
Sinusitis			
subjects affected / exposed	8 / 110 (7.27%)	3 / 109 (2.75%)	
occurrences (all)	10	6	

Herpes Zoster subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7	1 / 109 (0.92%) 1	
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	27 / 110 (24.55%) 31	32 / 109 (29.36%) 36	
Hyperglycaemia subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 10	6 / 109 (5.50%) 7	
Hyponatraemia subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 16	5 / 109 (4.59%) 7	
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 9	7 / 109 (6.42%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	The primary purpose of this amendment was to make following changes: Adjusted the study design to allow for randomization into two different study arms, each with a different dosing regimen (90 mg QD or 180 mg QD with a 7-day lead-in at 90 mg QD). Increased enrollment projections to fill both study arms (and added at least 6 more months to accrue participants). Updated the statistical testing methods to address both study arms. Updated clinical summary of data from the phase 1/2 study of brigatinib, including an assessment of respiratory events and reports of early onset pulmonary syndrome. Updated sections describing sampling for molecular genetic testing to allow for analysis of various tumor and plasma biomarkers as is feasible at different sites. Modified the wording of protocol eligibility criteria (Inclusion criteria 1, 2, 3, 6, 10 and 13; Exclusion criteria 6) to further clarify the type of participants to be enrolled. Updated the tissue and blood sample procedures (described separately) to occur only at screening and end-of-treatment for molecular genetics and added specifics for anaplastic lymphoma kinase (ALK) fluorescence in situ hybridization (FISH) testing. Updated the pharmacokinetic (PK) collection procedures to include slightly more frequent sampling in Cycles 3, 4, and 5. Updated Schedule of Events Table to include: randomization (on Day 1), a Day 8 visit, an assessment of brain MRI at screening, addition of ALK FISH testing (at screening), adjustments to descriptions of tissue and plasma sampling for molecular genetic testing. Added a section on continuing treatment after disease progression, by study arm. Added a section on re-escalation after dose modification. Added a section describing the Data Monitoring Committee. Updated the information in Appendix E (drugs with a risk of Torsades de Pointes). Made minor grammatical, punctuation, and spelling changes; updated per sponsor personnel changes; and updated all hyperlinks and access dates.
29 July 2014	The primary purpose of this amendment was to make following changes: Updated eligibility criteria (inclusion criteria 4, 6; Exclusion criteria 6, 7 and 16) to remove some restrictions on prior treatments, clarified restrictions for participants with central nervous system (CNS) activity, and added an exclusion for pregnant/breastfeeding women. Removed dietary restrictions based on clinical pharmacology testing results. Allowed for adding a couple additional postbaseline time points for plasma biomarker sampling. Updated the statistical sections to specify the analysis populations for efficacy and safety and clarified testing methodologies. Updated the description of procedures, as follows: added a reminder to monitor for visual dysfunction, added creatine kinase to the blood draw assessments and specified that all glucose and insulin draws should be fasted, added more frequent pregnancy testing, and specified a two-hour window for the final PK time point. Added guidelines for dose modifications (due to AEs) specific to QT prolongation, per the suggestion from a competent authority. Updated the AE severity definitions by removing relationship to study drug, which does not determine severity (general template change). Updated the definition of overdose and how to handle overdoses per standard reporting guidelines. Made minor grammatical, punctuation, and spelling changes and updated per sponsor personnel changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

