



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	29 February 2016

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	AP26113-13-201
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094573
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, Takeda Development Center Americas, Inc., +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda Development Center Americas, Inc., +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	Final
Date of interim/final analysis	29 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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	104

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 94 investigative sites in the United States, Canada, Europe, Australia and Asia from 04 Jun 2014 up to clinical cut-off date 29 Feb 2016. Study is ongoing.

Pre-assignment

Screening details:

Participants with ALK-positive, locally advanced or metastatic NSCLC who were treated with crizotinib were enrolled to receive AP26113 90 mg, once daily or AP26113 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.

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

Arm title	Brigatinib 90 mg - 180 mg
------------------	---------------------------

Arm description:

Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by AP26113 180 mg, orally once daily in Cycle 1 of 28 days followed by AP26113 180 mg, orally once daily in cycle 2 and onward cycles of 28 days until disease progression or intolerable toxicity.

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	7	1
Consent withdrawn by subject	2	4
Clinical Progressive Disease	4	3
Adverse event, non-fatal	3	9
Randomized but not treated	3	-
Ongoing	64	76
Non-compliance with study drug	-	1
Documented Progressive Disease	29	16

Baseline characteristics

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.

Reporting group title	Brigatinib 90 mg - 180 mg
-----------------------	---------------------------

Reporting group description:

Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by AP26113 180 mg, orally once daily in Cycle 1 of 28 days followed by AP26113 180 mg, orally once daily in cycle 2 and onward cycles of 28 days until disease progression or intolerable toxicity.

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	55.5	
standard deviation	± 13.01	± 12.96	-
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.	
Reporting group title	Brigatinib 90 mg - 180 mg
Reporting group description: Brigatinib 90 mg, tablets, orally, once daily for 7 days followed by AP26113 180 mg, orally once daily in Cycle 1 of 28 days followed by AP26113 180 mg, orally once daily in cycle 2 and onward cycles of 28 days until disease progression or intolerable toxicity.	

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 proportion of participants with confirmed Complete response (CR)/partial response (PR) per Response Evaluation Criteria in Solid tumors (RECIST) v1.1 (confirmed ≥ 4 weeks after initial response), after 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 30% decrease in sum of longest diameters (SLD) of target lesions, taking as reference baseline sum diameters. Intention to Treat (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	Primary
End point timeframe: Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 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: Statistical Analysis not reported for this endpoint.	

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%)	44.6 (34 to 55.6)	53.6 (42.6 to 64.5)		

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
-----------------	--

End point description:

ORR assessed by the IRC, is defined as the proportion of the participants with confirmed Clinical response (CR) or partial response (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 sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. The exact 2-sided 95% confidence interval was calculated. 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
----------------	-----------

End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 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%)	48.2 (38.7 to 57.9)	52.7 (43 to 62.3)		

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
-----------------	---

End point description:

Confirmed intracranial CNS ORR is defined as proportion 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 extranodal non-target lesions, 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 sum of longest diameters (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 assigned dose. Participants with measurable active brain metastases at baseline were evaluated for this endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 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	42.1 (20.3 to 66.5)	73.3 (44.9 to 92.2)		

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
-----------------	---

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. 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 at baseline were evaluated for this outcome measure. 99999 = Not applicable as upper limit of PFS was not reached.

End point type	Secondary
----------------	-----------

End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	51		
Units: months				
median (confidence interval 95%)	15.6 (7.3 to 15.7)	11.1 (7.4 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response
-----------------	------------------

End point description:

Time to response is 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 sum of the longest diameters (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 endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to data cut-off date: 29 Feb 2016 (approximately up to 20 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	59		
Units: months				
median (confidence interval 95%)	1.8 (1.7 to 9.1)	1.9 (1 to 11)		

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 time that measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that progressive disease is objectively documented or death. Patients without progressive disease or death were censored at the last valid response assessment. 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 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 endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to data cut-off date: 29 Feb 2016 (approximately up to 20 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	59		
Units: months				
median (confidence interval 95%)	13.8 (5.6 to 13.8)	11.1 (9.2 to 13.8)		

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 is 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 data cut-off date: 29 Feb 2016 (approximately up to 20 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				
arithmetic mean (standard deviation)	231.6 (± 129.19)	251.9 (± 137.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate
End point description:	
Disease control rate (DCR) is defined as the proportion 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 the 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 sum of the longest diameters (SLD) of target lesions, taking as reference the baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). 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

End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 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%)	82.1 (73.8 to 88.7)	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)
-----------------	---------------------------------

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). ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. 99999 = Not applicable, upper limit of PFS was not reached.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to data cut-off date: 29 Feb 2016 (approximately up to 20 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 15.6)	12.9 (11.1 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. ITT Population included all participants who were randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose. 9999 = Not applicable, The median OS and 95% CI were not reached due to relatively lower number of deaths occurred by the time of clinical cut-off date.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to data cut-off date: 29 Feb 2016 (approximately up to 20 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 (full range (min-max))				
Overall Survival	9999 (9999 to 9999)	9999 (9999 to 9999)		
1 Year Overall Survival	70.6 (59.8 to 79.1)	79.5 (66.9 to 87.7)		

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) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From first dose of study drug up to 30 days following the last dose of study drug (up to 20 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	106	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 Cycle 1 pre-dose; Cycle 2 pre-dose and at multiple time points (up to 6-8 hours) post dose; Cycles 3, 4 and 5 pre-dose and at 1-8 hours post 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)	520 (± 321.9)		
Cycle 3 (n=91, 92)	263.9 (± 238.9)	537 (± 360.3)		
Cycle 4 (n=80, 87)	236.1 (± 188)	564.7 (± 415)		
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
-----------------	---

End point description:

Patient-reported symptoms global health status/QoL scores were based on questions 29 and 30 of EORTC QLQ-C30. First 28 questions used 4-point scale (1=not at all,2=a little,3=quite a bit,4=very much) for evaluating 5 functional scales; 3 symptom scales; Last 2 questions on global health status/QoL scale are coded on 7-point scale (1=very poor-7=excellent). 6 single-item scales also are included. Raw scores for multi-item scales and single-item measures will be linearly transformed to obtain score ranging from 0-100, where higher score = a higher level of functioning. ITT Population included all participants who were randomized to each regimen regardless of whether they received

study drug or adhered to assigned dose. Here, n represents number of participants evaluable at specific time point. 99999 = No or only one participant was analyzed for time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 30 days after the last dose of study drug or up to data cut-off date: 29 Feb 2016 (approximately up to 20.2 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 (± 23.4)		
Cycle 2 (n=101, 97)	64.19 (± 20.73)	65.72 (± 19.54)		
Cycle 3 (n=91, 91)	65.57 (± 24.06)	68.5 (± 20.52)		
Cycle 4 (n=84, 89)	69.44 (± 20.59)	66.95 (± 20.89)		
Cycle 5 (n=82, 84)	70.12 (± 20.28)	72.12 (± 17.57)		
Cycle 6 (n=78, 81)	69.76 (± 20.02)	71.5 (± 18.63)		
Cycle 7 (n=75, 76)	67.56 (± 20.53)	71.05 (± 19.88)		
Cycle 8 (n=61, 70)	66.12 (± 22.46)	70.95 (± 19.95)		
Cycle 9 (n=53, 57)	67.77 (± 22.82)	70.32 (± 19.48)		
Cycle 10 (n=42, 47)	69.64 (± 22.07)	68.97 (± 22.43)		
Cycle 11 (n=29, 39)	69.54 (± 21.97)	69.87 (± 22.43)		
Cycle 12 (n=26, 33)	60.9 (± 24.47)	73.48 (± 23.15)		
Cycle 13 (n=20, 27)	65 (± 20.52)	74.07 (± 21.72)		
Cycle 14 (n=15, 22)	62.22 (± 24.57)	73.11 (± 22.56)		
Cycle 15 (n=12, 17)	64.58 (± 25.41)	74.02 (± 24.81)		
Cycle 16 (n=9,12)	64.81 (± 27.25)	74.31 (± 18.62)		
Cycle 17 (n=4, 7)	75 (± 11.79)	75 (± 24.06)		
Cycle 18 (n=1, 5)	100 (± 999999)	78.33 (± 21.73)		
Cycle 19 (n=0, 2)	999999 (± 999999)	66.67 (± 47.14)		
Cycle 20 (n=0,2)	999999 (± 999999)	70.83 (± 41.25)		
Cycle 21 (n=0,2)	999999 (± 999999)	62.5 (± 5.89)		
End of Treatment (n=30, 12)	37.78 (± 25.87)	48.61 (± 13.69)		

Follow-Up 30 Days After Last Dose (n=11, 10)	43.94 (± 32.93)	60 (± 15.61)		
---	-----------------	--------------	--	--

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
-----------------	--

End point description:

Confirmed intracranial CNS ORR: defined as proportion 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 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 with only non-measurable active brain metastases at baseline were evaluated for this endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Screening, at 8-week intervals thereafter (on Day 1 of every odd-numbered cycle) through 15 cycles and every 3 cycles thereafter until disease progression or up to data cut-off date: 29 Feb 2016 (approximately up to 20 months)

End point values	Brigatinib 90 mg	Brigatinib 90 mg - 180 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: percentage of participants				
number (confidence interval 95%)	9.4 (2 to 25)	19.4 (8.2 to 36)		

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 or up to data cut-off date: 29 Feb 2016 (approximately up to 20.2 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	12.0
--------------------	------

Reporting groups

Reporting group title	AP26113 90 mg - 180 mg
-----------------------	------------------------

Reporting group description:

AP26113 90 mg, tablets, orally, once daily for 7 days followed by AP26113 180 mg, orally once daily in Cycle 1 of 28 days followed by AP26113 180 mg, orally once daily in cycle 2 and onward cycles of 28 days until disease progression or intolerable toxicity.

Reporting group title	AP26113 90 mg
-----------------------	---------------

Reporting group description:

AP26113 90 mg, tablets, orally, once daily in each cycle of 28 days until disease progression or intolerable toxicity.

Serious adverse events	AP26113 90 mg - 180 mg	AP26113 90 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 110 (40.00%)	41 / 109 (37.61%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm Progression			
subjects affected / exposed	5 / 110 (4.55%)	13 / 109 (11.93%)	
occurrences causally related to treatment / all	0 / 5	0 / 14	
deaths causally related to treatment / all	0 / 5	0 / 10	
Malignant Pleural Effusion			
subjects affected / exposed	3 / 110 (2.73%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases To Central Nervous System			

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 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	
Vascular disorders			
Peripheral 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			
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	
General Physical Health Deterioration			
subjects affected / exposed	1 / 110 (0.91%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
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	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	8 / 110 (7.27%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	8 / 8	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 110 (1.82%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 110 (1.82%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
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	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	
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 / 0	
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	
Psychiatric disorders			
Confusional State			
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	

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	
Injury, poisoning and procedural complications			
Post Procedural Haemorrhage			
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	
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	
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	
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	
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 / 1	
Dysaesthesia			
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	
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	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	
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%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 / 1	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	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	
Transient Ischaemic Attack			
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	
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	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	
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	
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	
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	
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			
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%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
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	
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	
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	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 110 (7.27%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	1 / 9	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Appendicitis			
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	

Bronchitis			
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	
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	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	
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	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	
Metabolism and nutrition disorders			
Dehydration			
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	
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	

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	103 / 110 (93.64%)	103 / 109 (94.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 110 (20.91%)	12 / 109 (11.01%)	
occurrences (all)	41	15	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 110 (27.27%)	22 / 109 (20.18%)	
occurrences (all)	41	28	
Pyrexia			
subjects affected / exposed	7 / 110 (6.36%)	15 / 109 (13.76%)	
occurrences (all)	11	34	
Asthenia			
subjects affected / exposed	11 / 110 (10.00%)	9 / 109 (8.26%)	
occurrences (all)	18	10	
Oedema Peripheral			
subjects affected / exposed	8 / 110 (7.27%)	7 / 109 (6.42%)	
occurrences (all)	9	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 110 (33.64%)	20 / 109 (18.35%)	
occurrences (all)	47	31	
Dyspnoea			
subjects affected / exposed	21 / 110 (19.09%)	21 / 109 (19.27%)	
occurrences (all)	30	28	
Oropharyngeal Pain			
subjects affected / exposed	7 / 110 (6.36%)	8 / 109 (7.34%)	
occurrences (all)	7	8	
Dysphonia			
subjects affected / exposed	6 / 110 (5.45%)	5 / 109 (4.59%)	
occurrences (all)	8	17	

Productive Cough subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 6	5 / 109 (4.59%) 5	
Dyspnoea Exertional subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2	6 / 109 (5.50%) 6	
Haemoptysis subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 0	2 / 109 (1.83%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8	12 / 109 (11.01%) 13	
Investigations Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all)	33 / 110 (30.00%) 77	12 / 109 (11.01%) 27	
Amylase Increased subjects affected / exposed occurrences (all)	16 / 110 (14.55%) 22	9 / 109 (8.26%) 18	
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	16 / 110 (14.55%) 18	9 / 109 (8.26%) 12	
Lipase Increased subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 22	8 / 109 (7.34%) 13	
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 14	9 / 109 (8.26%) 9	
Blood Lactate Dehydrogenase Increased subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 11	2 / 109 (1.83%) 2	
Neutrophil Count Decreased subjects affected / exposed occurrences (all)	5 / 110 (4.55%) 7	6 / 109 (5.50%) 10	

Nervous system disorders			
Headache			
subjects affected / exposed	30 / 110 (27.27%)	30 / 109 (27.52%)	
occurrences (all)	50	59	
Dizziness			
subjects affected / exposed	9 / 110 (8.18%)	10 / 109 (9.17%)	
occurrences (all)	9	14	
Paraesthesia			
subjects affected / exposed	7 / 110 (6.36%)	10 / 109 (9.17%)	
occurrences (all)	9	12	
Peripheral Sensory Neuropathy			
subjects affected / exposed	7 / 110 (6.36%)	5 / 109 (4.59%)	
occurrences (all)	9	5	
Memory Impairment			
subjects affected / exposed	6 / 110 (5.45%)	2 / 109 (1.83%)	
occurrences (all)	6	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	10 / 110 (9.09%)	2 / 109 (1.83%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	44 / 110 (40.00%)	36 / 109 (33.03%)	
occurrences (all)	60	64	
Diarrhoea			
subjects affected / exposed	42 / 110 (38.18%)	21 / 109 (19.27%)	
occurrences (all)	120	28	
Vomiting			
subjects affected / exposed	25 / 110 (22.73%)	26 / 109 (23.85%)	
occurrences (all)	56	47	
Constipation			
subjects affected / exposed	17 / 110 (15.45%)	21 / 109 (19.27%)	
occurrences (all)	27	25	
Abdominal Pain			
subjects affected / exposed	9 / 110 (8.18%)	17 / 109 (15.60%)	
occurrences (all)	12	21	
Stomatitis			

subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 12	4 / 109 (3.67%) 5	
Dyspepsia subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 8	7 / 109 (6.42%) 7	
Dry Mouth subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 10	2 / 109 (1.83%) 2	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	18 / 110 (16.36%) 0	8 / 109 (7.34%) 0	
Pruritus subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 9	6 / 109 (5.50%) 6	
Dermatitis Acneiform subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 3	6 / 109 (5.50%) 7	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6	0 / 109 (0.00%) 0	
Musculoskeletal and connective tissue disorders Muscle Spasms subjects affected / exposed occurrences (all)	19 / 110 (17.27%) 27	13 / 109 (11.93%) 20	
Arthralgia subjects affected / exposed occurrences (all)	15 / 110 (13.64%) 19	15 / 109 (13.76%) 19	
Back Pain subjects affected / exposed occurrences (all)	17 / 110 (15.45%) 20	10 / 109 (9.17%) 16	
Pain in extremity subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 5	12 / 109 (11.01%) 14	
Myalgia			

subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 12	6 / 109 (5.50%) 7	
Musculoskeletal Pain subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 12	4 / 109 (3.67%) 5	
Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 12	5 / 109 (4.59%) 5	
Neck Pain subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 8	2 / 109 (1.83%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 110 (8.18%) 14	9 / 109 (8.26%) 9	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7	8 / 109 (7.34%) 6	
Urinary Tract Infection subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 6	6 / 109 (5.50%) 8	
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	17 / 110 (15.45%) 23	24 / 109 (22.02%) 27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	<ul style="list-style-type: none">• Adjusted 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 patients).• Updated 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 the 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.• Updated tissue and blood sample procedures (described separately) to occur only at screening and end-of-treatment for molecular genetics, and added specifics for ALK FISH testing.• Updated 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, the addition of ALK FISH testing (at screening), adjustments to the descriptions of tissue and plasma sampling for molecular genetic testing, clarified the general description of assessments done every 8 weeks, and noted that an assessment of pulmonary symptoms should be performed during the visit on Day 8 and Day 15.• Updated dose modification sections (for TEAEs) to include separate recommendations for each study arm: one for Arm A and two for Arm B (one at 90 mg in the first 7 days and one after dose escalation to 180 mg).• Added a section on management of treatment-related early onset pulmonary syndrome and added updates to further clarify the section on management of treatment-related pneumonitis.• Added a section on re-escalation after dose modification.• Added a section describing Data Monitoring Committee.
29 July 2014	<ul style="list-style-type: none">• Updated eligibility criteria to remove some restrictions on prior treatments, clarified restrictions for patients with 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported