



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 |
|-----------------------|----------------|

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 |
|------------------|---------------------------|

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 |
|-----------------------|------------------|

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).

| 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) |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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

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. 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 |
|----------------|-----------|

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 |
|-----------------|------------------|

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 |
|----------------|-----------|

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)

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|---|----------------------------|
| 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) |
|-----------------|---------------------------------|

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 |
|----------------|-----------|

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) |
|-----------------|-----------------------|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | AP26113 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).

| | |
|-----------------------|---------------|
| Reporting group title | AP26113 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).

| 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

