



## Clinical trial results:

### Brigatinib in Patients With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2018-000635-27    |
| Trial protocol           | SE DE ES AT NL IT |
| Global end of trial date | 21 August 2024    |

#### Results information

|                                |                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                    |
| This version publication date  | 17 August 2025                                                                                                  |
| First version publication date | 26 June 2025                                                                                                    |
| Version creation reason        | <ul style="list-style-type: none"><li>Correction of full data set</li></ul> Update in total All-Cause Mortality |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | Brigatinib-2002 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03535740 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                     |
|------------------------------|-----------------------------------------------------|
| Sponsor organisation name    | Takeda                                              |
| Sponsor organisation address | 95 Hayden Ave, Lexington, MA, United States, 02421  |
| Public contact               | Study Director, Takeda, TrialDisclosures@takeda.com |
| Scientific contact           | Study Director, Takeda, 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                       | 21 August 2024 |
| Is this the analysis of the primary completion data? | No             |

|                                  |                |
|----------------------------------|----------------|
| Global end of trial reached?     | Yes            |
| Global end of trial date         | 21 August 2024 |
| Was the trial ended prematurely? | No             |

Notes:

## General information about the trial

Main objective of the trial:

The main aim of this study is to determine the efficacy of brigatinib in participants with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 31 January 2019 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 6              |
| Country: Number of subjects enrolled | United States: 7       |
| Country: Number of subjects enrolled | Austria: 1             |
| Country: Number of subjects enrolled | France: 7              |
| Country: Number of subjects enrolled | Germany: 3             |
| Country: Number of subjects enrolled | Italy: 16              |
| Country: Number of subjects enrolled | Netherlands: 2         |
| Country: Number of subjects enrolled | Spain: 11              |
| Country: Number of subjects enrolled | Sweden: 2              |
| Country: Number of subjects enrolled | China: 14              |
| Country: Number of subjects enrolled | Hong Kong: 6           |
| Country: Number of subjects enrolled | Japan: 3               |
| Country: Number of subjects enrolled | Korea, Republic of: 20 |
| Country: Number of subjects enrolled | Taiwan: 4              |
| Country: Number of subjects enrolled | Australia: 1           |
| Worldwide total number of subjects   | 103                    |
| EEA total number of subjects         | 42                     |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 80 |
| From 65 to 84 years                       | 23 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 54 investigative sites in Canada, United States, Austria, France, Germany, Italy, Netherlands, Spain, Sweden, China, Hong Kong, Japan, Korea, Taiwan, and Australia from 31 January 2019 to 21 August 2024.

### Pre-assignment

Screening details:

Subjects with ALK+, advanced NSCLC were enrolled to receive brigatinib 90mg followed by 180mg up to disease progression. 102 subjects discontinued study upto interim data cut-off date: 20 May 2021, by then all study outcome measures were met & data collection was complete. 1 subject stayed on until study completion as mean to provide access to brigatinib.

### Period 1

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

### Arms

|           |                                                                |
|-----------|----------------------------------------------------------------|
| Arm title | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |
|-----------|----------------------------------------------------------------|

Arm description:

Participants received brigatinib 90 mg, tablets, orally, once daily (QD) for 7 days, followed by brigatinib 180 mg, tablets, orally, QD for until objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, or intolerable toxicity. Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD based on investigator's discretion, up to 28 months from start of enrollment until data cut-off: 20 May 2021.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Brigatinib      |
| Investigational medicinal product code | Brigatinib-2002 |
| Other name                             | AP26113         |
| Pharmaceutical forms                   | Capsule         |
| Routes of administration               | Oral use        |

Dosage and administration details:

Participants received brigatinib 90 mg, tablets, orally, once daily for 7 days, followed by brigatinib 180 mg, tablets, orally, once daily.

|                                            |                                                                |
|--------------------------------------------|----------------------------------------------------------------|
| Number of subjects in period 1             | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |
| Started                                    | 103                                                            |
| Participants who received brigatinib 240mg | 13                                                             |
| Completed                                  | 0                                                              |
| Not completed                              | 103                                                            |
| Adverse event, serious fatal               | 44                                                             |
| Consent withdrawn by subject               | 13                                                             |

|                            |    |
|----------------------------|----|
| Site Terminated by Sponsor | 45 |
| Lost to follow-up          | 1  |

## Baseline characteristics

### Reporting groups

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |
|-----------------------|----------------------------------------------------------------|

Reporting group description:

Participants received brigatinib 90 mg, tablets, orally, once daily (QD) for 7 days, followed by brigatinib 180 mg, tablets, orally, QD for until objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, or intolerable toxicity. Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD based on investigator's discretion, up to 28 months from start of enrollment until data cut-off: 20 May 2021.

| Reporting group values             | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg | Total |  |
|------------------------------------|----------------------------------------------------------------|-------|--|
| Number of subjects                 | 103                                                            | 103   |  |
| Age Categorical<br>Units: Subjects |                                                                |       |  |

|                                                                            |                    |    |  |
|----------------------------------------------------------------------------|--------------------|----|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation    | 54.7<br>± 11.94    | -  |  |
| Gender categorical<br>Units: Subjects                                      |                    |    |  |
| Male                                                                       | 51                 | 51 |  |
| Female                                                                     | 52                 | 52 |  |
| Ethnicity<br>Units: Subjects                                               |                    |    |  |
| Hispanic or Latino                                                         | 2                  | 2  |  |
| Not Hispanic or Latino                                                     | 92                 | 92 |  |
| Unknown or Not Reported                                                    | 9                  | 9  |  |
| Race<br>Units: Subjects                                                    |                    |    |  |
| American Indian or Alaska Native                                           | 0                  | 0  |  |
| Asian                                                                      | 49                 | 49 |  |
| Native Hawaiian or Other Pacific Islander                                  | 0                  | 0  |  |
| White                                                                      | 44                 | 44 |  |
| More than one race                                                         | 0                  | 0  |  |
| Unknown or Not Reported                                                    | 9                  | 9  |  |
| Black or African American                                                  | 1                  | 1  |  |
| Height<br>Units: centimetres (cm)<br>arithmetic mean<br>standard deviation | 165.86<br>± 10.172 | -  |  |
| Weight<br>Units: kilograms (kg)<br>arithmetic mean                         | 69.23              |    |  |

|                    |              |   |  |
|--------------------|--------------|---|--|
| standard deviation | $\pm 15.409$ | - |  |
|--------------------|--------------|---|--|

## End points

### End points reporting groups

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |
|-----------------------|----------------------------------------------------------------|

#### Reporting group description:

Participants received brigatinib 90 mg, tablets, orally, once daily (QD) for 7 days, followed by brigatinib 180 mg, tablets, orally, QD for until objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, or intolerable toxicity. Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD based on investigator's discretion, up to 28 months from start of enrollment until data cut-off: 20 May 2021.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Brigatinib 90/180 mg |
| Subject analysis set type  | Full analysis        |

#### Subject analysis set description:

Brigatinib 90 mg, tablets, orally, QD for 7 days, followed by Brigatinib 180 mg, tablets, orally, QD for until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity up to approximately 28 months from start of enrollment till data cut-off: 20 May 2021. Participants who experienced progression on any doses but judged as still benefiting from the study treatment by the investigator continued to use the current dose, up to study end.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Brigatinib 240 mg  |
| Subject analysis set type  | Sub-group analysis |

#### Subject analysis set description:

Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD from start of enrollment based on investigator's discretion up to data-cut off: 20 May 2021 (approximately 28 months). Participants who experienced progression on any doses but judged as still benefiting from the study treatment by the investigator continued to use the current dose, up to study end.

### Primary: Confirmed Objective Response Rate (ORR) Using RECIST v1.1 as Assessed by the Independent Review Committee (IRC)

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Confirmed Objective Response Rate (ORR) Using RECIST v1.1 as Assessed by the Independent Review Committee (IRC) <sup>[1]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Confirmed ORR is defined as the percentage of the participants who are confirmed to have achieved complete response (CR) or partial response (PR), per RECIST version 1.1 (confirmed  $\geq 4$  weeks after initial response), after the initiation of study treatment. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to  $< 10$  mm in short axis and PR: at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions taking as reference the Baseline sum diameters. Percentages were rounded off to the nearest single decimal place. Full Analysis Population included all participants who received at least 1 dose of brigatinib.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Up to approximately 20 months from the start of enrollment till data cut-off 30 September 2020

#### 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: Single arm statistical analysis was performed but is not reported here to prevent an error. The p-value was 0.0763 and was based on the comparison of the confirm ORR among the 90/180mg group against a fixed response rate of 20%. The calculation was based on an exact binomial test with a total 1-sided alpha level of 0.025 at primary analysis.



|                                   |                                                                |  |  |  |
|-----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                | Reporting group                                                |  |  |  |
| Number of subjects analysed       | 103                                                            |  |  |  |
| Units: percentage of participants |                                                                |  |  |  |
| number (confidence interval 95%)  | 26.2 (18.0 to 35.8)                                            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Confirmed ORR Using RECIST v1.1 as Assessed by the Investigator

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Confirmed ORR Using RECIST v1.1 as Assessed by the Investigator |
|-----------------|-----------------------------------------------------------------|

End point description:

Confirmed ORR is defined as the percentage of the participants who are confirmed to have achieved CR or PR, per RECIST version 1.1 (confirmed  $\geq 4$  weeks after initial response), after the initiation of study treatment. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to  $<10$  mm in short axis and PR: at least a 30% decrease in the SLD of target lesions taking as reference the baseline sum diameters. Percentages were rounded off to the nearest single decimal place. Full Analysis Population included all participants who received at least 1 dose of brigatinib.

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

End point timeframe:

Up to approximately 28 months

|                                   |                                                                |  |  |  |
|-----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                | Reporting group                                                |  |  |  |
| Number of subjects analysed       | 103                                                            |  |  |  |
| Units: percentage of participants |                                                                |  |  |  |
| number (confidence interval 95%)  | 26.2 (18.0 to 35.8)                                            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR) as Assessed by the IRC and the Investigator

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Duration of Response (DOR) as Assessed by the IRC and the Investigator |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                        |
| DOR is defined as the time interval from the time that the measurement criteria are first met for CR or PR until the first date that the progressive disease (PD) is objectively documented, or death. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. PR: at least a 30% decrease in the SLD of target lesions taking as reference the Baseline sum diameters. PD: SLD increased by at least 20% from the smallest value on study (including Baseline, if that is the smallest). SLD must also demonstrate an absolute increase of at least 5 mm (2 lesions increasing from, for example, 2 mm to 3 mm, does not qualify). Full Analysis Population included all participants who received at least 1 dose of brigatinib. Subjects analysed: number of participants who were responders. '999' indicates: upper limit of 95 % confidence interval was not estimable due to insufficient number of events observed among responding participants. |                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                        |
| Up to approximately 28 months                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                        |

|                                  |                                                                |  |  |  |
|----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type               | Reporting group                                                |  |  |  |
| Number of subjects analysed      | 27                                                             |  |  |  |
| Units: months                    |                                                                |  |  |  |
| number (confidence interval 95%) |                                                                |  |  |  |
| IRC-Assessed DOR                 | 6.341 (5.552 to 999)                                           |  |  |  |
| Investigator-Assessed DOR        | 6.735 (4.435 to 9.232)                                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-Free Survival (PFS) as Assessed by the IRC and the Investigator

|                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                              | Progression-Free Survival (PFS) as Assessed by the IRC and the Investigator |
| 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. PFS was censored for participants without documented disease progression or death. Full Analysis Population included all participants who received at least 1 dose of brigatinib. |                                                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                                                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                         |                                                                             |
| Up to approximately 28 Months                                                                                                                                                                                                                                                                                                                                                                                |                                                                             |

|                                  |                                                                |  |  |  |
|----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type               | Reporting group                                                |  |  |  |
| Number of subjects analysed      | 103                                                            |  |  |  |
| Units: months                    |                                                                |  |  |  |
| number (confidence interval 95%) |                                                                |  |  |  |
| IRC-Assessed PFS                 | 3.811 (3.515 to 5.848)                                         |  |  |  |
| Investigator-Assessed PFS        | 3.811 (3.154 to 5.552)                                         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR) as Assessed by the IRC and the Investigator

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Disease Control Rate (DCR) as Assessed by the IRC and the Investigator |
|-----------------|------------------------------------------------------------------------|

End point description:

DCR is defined as the percentage of participants who have achieved CR, PR or stable disease (SD) (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study treatment. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. PR: at least a 30% decrease in the 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 PD. Percentages were rounded off to the nearest single decimal place. Full Analysis Population included all participants who received at least 1 dose of brigatinib.

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

End point timeframe:

Up to approximately 28 months

|                                   |                                                                |  |  |  |
|-----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                | Reporting group                                                |  |  |  |
| Number of subjects analysed       | 103                                                            |  |  |  |
| Units: percentage of participants |                                                                |  |  |  |
| number (confidence interval 95%)  |                                                                |  |  |  |
| IRC-Assessed DCR                  | 54.4 (44.3 to 64.2)                                            |  |  |  |
| Investigator-Assessed DCR         | 59.2 (49.1 to 68.8)                                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response as Assessed by the IRC and the Investigator

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Time to Response as Assessed by the IRC and the Investigator |
|-----------------|--------------------------------------------------------------|

End point description:

Time to response is defined as the time interval from the date of the first dose of the study treatment until the initial observation of CR or PR. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. PR: at least a 30% decrease in the SLD of target lesions taking as reference the baseline sum diameters. Full Analysis Population included all participants who received at least 1 dose of brigatinib. Subjects analysed is the number of participants who were responders.

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

End point timeframe:

Up to approximately 28 months

|                                        |                                                                |  |  |  |
|----------------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>                | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                     | Reporting group                                                |  |  |  |
| Number of subjects analysed            | 27                                                             |  |  |  |
| Units: months                          |                                                                |  |  |  |
| number (confidence interval 95%)       |                                                                |  |  |  |
| IRC-Assessed Time to Response          | 1.807 (1.45 to 5.36)                                           |  |  |  |
| Investigator-Assessed Time to Response | 1.807 (1.58 to 10.87)                                          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Confirmed Intracranial Objective Response Rate (iORR) in Participants With Brain Metastases at Baseline, as Assessed by the IRC

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Confirmed Intracranial Objective Response Rate (iORR) in Participants With Brain Metastases at Baseline, as Assessed by the IRC |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

Confirmed iORR is defined as the proportion of the participants who have achieved CR or PR in the brain per a modification of RECIST version 1.1, after the initiation of study treatment, in participants with intracranial brain metastases at baseline. CR: disappearance of all extranodal target lesions and all pathological lymph nodes must have decreased to <10 mm in short axis. or partial response or PR: at least a 30% decrease in the SLD of target lesions taking as reference the baseline sum diameters. Percentages were rounded off to the nearest single decimal place. Intracranial central nervous system (iCNS) disease population included those participants in the Full Analysis Population who were determined by the IRC to have iCNS metastases at baseline, regardless of whether they had at least 1 lesion that qualified as a target lesion in their baseline assessment by the IRC.

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

End point timeframe:  
Up to approximately 28 months

|                                   |                                                                |  |  |  |
|-----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                | Reporting group                                                |  |  |  |
| Number of subjects analysed       | 55                                                             |  |  |  |
| Units: percentage of participants |                                                                |  |  |  |
| number (confidence interval 95%)  | 14.5 (6.5 to 26.7)                                             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Intracranial Response in Participants With Brain Metastases at Baseline, as Assessed by the IRC

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Duration of Intracranial Response in Participants With Brain Metastases at Baseline, as Assessed by the IRC |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Duration of intracranial response: time interval from time that measurement criteria are first met for CR/PR until first date that PD (including baseline, if that is smallest). SLD must also demonstrate an absolute increase of at least 5mm. (2 lesions increasing from, for example, 2mm-3mm, does not qualify) in brain is objectively documented/death, in participants with intracranial metastases at baseline. CR: disappearance of all extranodal target lesions & all pathological lymph nodes must have decreased to <10 mm in short axis/partial response/PR: at least a 30% decrease in SLD of target lesions taking as reference baseline sum diameters in brain. PD: SLD increased by at least 20% from smallest value on study. Analysis population: iCNS disease population. Subjects analysed: subjects who were responders. '9999' indicates the median and upper limit of 95 % confidence interval was not estimable due to insufficient number of events observed among the responding participants.

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

End point timeframe:

Up to approximately 28 months

|                                  |                                                                |  |  |  |
|----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type               | Reporting group                                                |  |  |  |
| Number of subjects analysed      | 8                                                              |  |  |  |
| Units: months                    |                                                                |  |  |  |
| median (confidence interval 95%) | 9999 (5.717 to 9999)                                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Intracranial Progression-Free Survival (iPFS) in Participants With Brain Metastases at Baseline, as Assessed by the IRC

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Intracranial Progression-Free Survival (iPFS) in Participants With Brain Metastases at Baseline, as Assessed by the IRC |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

iPFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which intracranial brain disease progression is objectively documented, or death due to any cause, whichever occurs first, in participants with intracranial metastases at enrollment. iPFS were censored for participants without documented intracranial disease progression or death. iCNS disease population included of those participants in the Full Analysis Population who were determined by the IRC to have iCNS metastases at baseline, regardless of whether they had at least 1 lesion that qualified as a target lesion in their Baseline assessment by the IRC.

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

End point timeframe:

Up to approximately 28 months

|                                  |                                                                |  |  |  |
|----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type               | Reporting group                                                |  |  |  |
| Number of subjects analysed      | 55                                                             |  |  |  |
| Units: months                    |                                                                |  |  |  |
| median (confidence interval 95%) | 5.224 (3.515 to 7.392)                                         |  |  |  |

## 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. It was censored on the date of last contact for those participants who were alive. Full Analysis Population included all participants who received at least 1 dose of brigatinib. '99999' indicates that the upper limit of 95 % confidence interval was not estimable due to insufficient number of events observed among the responding participants.

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

End point timeframe:  
Up to approximately 28 months

|                                  |                                                                |  |  |  |
|----------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type               | Reporting group                                                |  |  |  |
| Number of subjects analysed      | 103                                                            |  |  |  |
| Units: months                    |                                                                |  |  |  |
| median (confidence interval 95%) | 21.290 (12.189 to 99999)                                       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With One or More Treatment-emergent Adverse Event (TEAE)

|                 |                                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Number of Participants With One or More Treatment-emergent Adverse Event (TEAE) |
|-----------------|---------------------------------------------------------------------------------|

End point description:

AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. TEAE: any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days of the last administration of study drug. Safety Analysis Population included all participants who received at least 1 dose of brigatinib. As pre-specified in protocol, AEs are reported for 2 sets/arms. Arm 1 (brigatinib 90/180 mg) and Arm 2 (brigatinib 240 mg).

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

End point timeframe:

First dose of study drug up to 30 days after last dose (approximately 5 years)

|                             |                      |                      |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>     | Brigatinib 90/180 mg | Brigatinib 240 mg    |  |  |
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 103                  | 13                   |  |  |
| Units: participants         | 103                  | 12                   |  |  |

### Statistical analyses

## Secondary: Number of Participants With Improvement in Health-Related Quality of Life (HRQOL) Based on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Improvement in Health-Related Quality of Life (HRQOL) Based on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

EORTC QLQ-C30 incorporates 5 functional scales(physical functioning,role functioning,emotional functioning,cognitive functioning,&social functioning),1 global health status scale, 3 symptom scales(fatigue, nausea&vomiting,& pain),&6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea,& financial difficulties). EORTC QLQ-C30 contains 28 questions (4-point scale where 1=Not at all [best] to 4=Very Much [worst]) &2 questions (7-point scale where 1=Very poor [worst] to 7=Excellent [best]). Raw scores are converted into scale scores ranging from 0 to 100. For functional scales&global health status scale, higher scores: better quality of life (QOL); for symptom scales, lower scores represent better QOL. Improvement:change from baseline of 10/more points higher for functional scales&10/more points lower for symptom scales.FAS.Subjects analysed:participants with data available for analysis.'n': number of participants with data available for analysis for specified category.

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

### End point timeframe:

Up to approximately 28 months

|                                              |                                                                |  |  |  |
|----------------------------------------------|----------------------------------------------------------------|--|--|--|
| <b>End point values</b>                      | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
| Subject group type                           | Reporting group                                                |  |  |  |
| Number of subjects analysed                  | 93                                                             |  |  |  |
| Units: participants                          |                                                                |  |  |  |
| Global Health Status/QoL(n=93)               | 52                                                             |  |  |  |
| Physical Functioning (n=93)                  | 55                                                             |  |  |  |
| Role Functioning (n=93)                      | 53                                                             |  |  |  |
| Role Functioning Emotional Functioning(n=93) | 36                                                             |  |  |  |
| Cognitive Functioning (n=93)                 | 47                                                             |  |  |  |
| Social Functioning (n=93)                    | 53                                                             |  |  |  |
| Fatigue (n=93)                               | 55                                                             |  |  |  |
| Nausea and Vomiting(n=93)                    | 21                                                             |  |  |  |
| Pain (n=93)                                  | 48                                                             |  |  |  |
| Dyspnoea Raw(n=93)                           | 26                                                             |  |  |  |
| Insomnia (n=93)                              | 40                                                             |  |  |  |
| Appetite Loss (n=93)                         | 30                                                             |  |  |  |
| Constipation (n=92)                          | 23                                                             |  |  |  |
| Diarrhoea (n=93)                             | 27                                                             |  |  |  |
| Financial Difficulties(n=93)                 | 27                                                             |  |  |  |

## Statistical analyses



**Secondary: Number of Participants With Improvement of HRQOL Based on EORTC QLQ- Lung Cancer (LC) 13**

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Improvement of HRQOL Based on EORTC QLQ- Lung Cancer (LC) 13 |
|-----------------|------------------------------------------------------------------------------------------|

## End point description:

HRQOL scores was assessed with EORTC, its lung cancer module QLQ-LC13. QLQ-LC13 contains 13 questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and use of pain medication. Scale score range: 0 to 100. Higher symptom score = greater degree of symptom severity. Improvement is defined as a change from baseline of 10 or more points lower for symptom scales. Full Analysis Population included all participants who received at least 1 dose of brigatinib. Subjects analysed is the number of participants with data available for analysis. 'n' indicates the number of participants with data available for analysis for the specified category.

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

## End point timeframe:

Up to approximately 28 months

| End point values                | Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg |  |  |  |
|---------------------------------|----------------------------------------------------------------|--|--|--|
| Subject group type              | Reporting group                                                |  |  |  |
| Number of subjects analysed     | 93                                                             |  |  |  |
| Units: participants             |                                                                |  |  |  |
| Composite Endpoint Score (n=93) | 61                                                             |  |  |  |
| Dyspnoea (n=93)                 | 45                                                             |  |  |  |
| Coughing (n=93)                 | 37                                                             |  |  |  |
| Haemoptysis (n=93)              | 4                                                              |  |  |  |
| Sore Mouth (n=93)               | 6                                                              |  |  |  |
| Dysphagia (n=93)                | 4                                                              |  |  |  |
| Peripheral Neuropathy (n=93)    | 25                                                             |  |  |  |
| Alopecia (n=93)                 | 14                                                             |  |  |  |
| Pain in Chest (n=93)            | 24                                                             |  |  |  |
| Pain in Arm or Shoulder (n=93)  | 23                                                             |  |  |  |
| Pain in Other Parts (n=92)      | 41                                                             |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to 30 days after last dose (approximately 5 years)

Adverse event reporting additional description:

Safety Analysis Population: participants who received at least 1 dose of brigatinib. As pre-specified in protocol, all-cause mortality and AEs are reported separately for 2 sets/arms: Arm 1 (brigatinib 90/180 mg) and Arm 2 (brigatinib 240 mg).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

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

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Brigatinib 240 mg |
|-----------------------|-------------------|

Reporting group description:

Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD from start of enrolment based on investigator's discretion up to data-cut off: 30 September 2020 (approximately 20 months). Participants who experienced progression on any doses but judged as still benefiting from the study treatment by the investigator may continue to use the current dose, up to study end.

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

Reporting group description:

Participants received brigatinib 90 mg, tablets, orally, QD for 7 days, followed by brigatinib 180 mg, tablets, orally, QD for until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity. Participants who experienced progression on the 180 mg dose and had not experienced toxicities greater than Grade 2 had the option to receive brigatinib 240 mg QD based on investigator's discretion, up to 28 months from start of enrollment until data cut-off: 20 May 2021. 1 Participant who experienced progression on any doses but judged as still benefiting from the study treatment by the investigator continued to receive brigatinib 180 mg, tablets, orally, once daily up to study end.

| Serious adverse events                                              | Brigatinib 240 mg | Brigatinib 90/180 mg |  |
|---------------------------------------------------------------------|-------------------|----------------------|--|
| Total subjects affected by serious adverse events                   |                   |                      |  |
| subjects affected / exposed                                         | 3 / 13 (23.08%)   | 48 / 103 (46.60%)    |  |
| number of deaths (all causes)                                       | 5                 | 39                   |  |
| number of deaths resulting from adverse events                      | 0                 | 17                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                      |  |
| Cancer pain                                                         |                   |                      |  |
| subjects affected / exposed                                         | 0 / 13 (0.00%)    | 1 / 103 (0.97%)      |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                |  |
| Lung neoplasm malignant                                             |                   |                      |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metastases to biliary tract                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metastases to central nervous system            |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Metastases to meninges                          |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Neoplasm progression                            |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Non-small cell lung cancer                      |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| Tumour associated fever                         |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vascular disorders                              |                |                 |  |
| Hypovolaemic shock                              |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Deep vein thrombosis                            |                |                 |  |

|                                                      |                |                 |  |
|------------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Hypertension                                         |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 3 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Surgical and medical procedures                      |                |                 |  |
| Hospitalisation                                      |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Pyrexia                                              |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pain                                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Peripheral swelling                                  |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General physical health deterioration                |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1           |  |
| Fatigue                                              |                |                 |  |
| subjects affected / exposed                          | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| Disease progression                             |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Death                                           |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Complication of device insertion                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Bronchial haemorrhage                           |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dyspnoea                                        |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 4 / 103 (3.88%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 3           |  |
| Malignant pleural effusion                      |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pleural effusion                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonitis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| Pulmonary artery thrombosis                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary oedema                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory failure                             |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Pulmonary embolism                              |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Investigations                                  |                |                 |  |
| Liver function test abnormal                    |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| 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  |                |                 |  |
| Craniofacial fracture                           |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac disorders                               |                |                 |  |
| Cardiac failure                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac arrest                                  |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Atrial flutter                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |
| Spinal cord compression                         |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cerebral haemorrhage                            |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Epilepsy                                        |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 103 (1.94%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Ischaemic stroke                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Moyamoya disease                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Paraesthesia                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sciatica                                        |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Seizure                                         |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 3 / 103 (2.91%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Neutropenia                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thrombocytopenia                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Duodenal obstruction                            |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intestinal obstruction                          |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Dysuria                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 103 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Intervertebral disc protrusion                  |                |                 |  |



|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Back pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Arthralgia                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Appendicitis                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Abdominal sepsis                                |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Sepsis                                          |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory tract infection                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonia                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 5 / 103 (4.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Meningitis                                      |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infectious pleural effusion                     |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cellulitis                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metabolism and nutrition disorders              |                |                 |  |
| Hyperkalaemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyperglycaemia                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypercalcaemia                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gout                                            |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dehydration                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 103 (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                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyponatraemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 103 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Brigatinib 240 mg | Brigatinib 90/180 mg |  |
|-------------------------------------------------------|-------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                   |                      |  |
| subjects affected / exposed                           | 12 / 13 (92.31%)  | 98 / 103 (95.15%)    |  |
| Vascular disorders                                    |                   |                      |  |
| Hypertension                                          |                   |                      |  |
| subjects affected / exposed                           | 3 / 13 (23.08%)   | 20 / 103 (19.42%)    |  |
| occurrences (all)                                     | 4                 | 32                   |  |
| General disorders and administration site conditions  |                   |                      |  |
| Swelling face                                         |                   |                      |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)    | 0 / 103 (0.00%)      |  |
| occurrences (all)                                     | 1                 | 0                    |  |
| Oedema peripheral                                     |                   |                      |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)    | 8 / 103 (7.77%)      |  |
| occurrences (all)                                     | 1                 | 9                    |  |
| Non-cardiac chest pain                                |                   |                      |  |
| subjects affected / exposed                           | 0 / 13 (0.00%)    | 8 / 103 (7.77%)      |  |
| occurrences (all)                                     | 0                 | 9                    |  |
| Fatigue                                               |                   |                      |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)    | 4 / 103 (3.88%)      |  |
| occurrences (all)                                     | 1                 | 4                    |  |
| Chest pain                                            |                   |                      |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)    | 4 / 103 (3.88%)      |  |
| occurrences (all)                                     | 1                 | 4                    |  |
| Asthenia                                              |                   |                      |  |

|                                                                                                                                 |                                 |                                    |  |
|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                     | <p>3 / 13 (23.08%)</p> <p>5</p> | <p>13 / 103 (12.62%)</p> <p>15</p> |  |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                      | <p>2 / 13 (15.38%)</p> <p>2</p> | <p>13 / 103 (12.62%)</p> <p>15</p> |  |
| <p>Mucosal inflammation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                         | <p>2 / 13 (15.38%)</p> <p>3</p> | <p>2 / 103 (1.94%)</p> <p>2</p>    |  |
| <p>Immune system disorders</p> <p>Cytokine release syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>     | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>0 / 103 (0.00%)</p> <p>0</p>    |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 13 (23.08%)</p> <p>3</p> | <p>25 / 103 (24.27%)</p> <p>30</p> |  |
| <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                    | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>3 / 103 (2.91%)</p> <p>5</p>    |  |
| <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                     | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>12 / 103 (11.65%)</p> <p>16</p> |  |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                         | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>6 / 103 (5.83%)</p> <p>6</p>    |  |
| <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                     | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>3 / 103 (2.91%)</p> <p>3</p>    |  |
| <p>Persistent depressive disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                               | <p>1 / 13 (7.69%)</p> <p>1</p>  | <p>0 / 103 (0.00%)</p> <p>0</p>    |  |
| <p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>     | <p>2 / 13 (15.38%)</p> <p>2</p> | <p>19 / 103 (18.45%)</p> <p>31</p> |  |

|                                        |                 |                   |
|----------------------------------------|-----------------|-------------------|
| Amylase increased                      |                 |                   |
| subjects affected / exposed            | 2 / 13 (15.38%) | 16 / 103 (15.53%) |
| occurrences (all)                      | 2               | 35                |
| Aspartate aminotransferase increased   |                 |                   |
| subjects affected / exposed            | 3 / 13 (23.08%) | 22 / 103 (21.36%) |
| occurrences (all)                      | 4               | 35                |
| Blood alkaline phosphatase increased   |                 |                   |
| subjects affected / exposed            | 0 / 13 (0.00%)  | 9 / 103 (8.74%)   |
| occurrences (all)                      | 0               | 14                |
| Blood bilirubin increased              |                 |                   |
| subjects affected / exposed            | 1 / 13 (7.69%)  | 0 / 103 (0.00%)   |
| occurrences (all)                      | 1               | 0                 |
| Blood calcium increased                |                 |                   |
| subjects affected / exposed            | 1 / 13 (7.69%)  | 2 / 103 (1.94%)   |
| occurrences (all)                      | 1               | 2                 |
| Blood cholesterol increased            |                 |                   |
| subjects affected / exposed            | 2 / 13 (15.38%) | 5 / 103 (4.85%)   |
| occurrences (all)                      | 2               | 7                 |
| Blood creatine phosphokinase increased |                 |                   |
| subjects affected / exposed            | 5 / 13 (38.46%) | 35 / 103 (33.98%) |
| occurrences (all)                      | 7               | 87                |
| Blood creatinine increased             |                 |                   |
| subjects affected / exposed            | 1 / 13 (7.69%)  | 5 / 103 (4.85%)   |
| occurrences (all)                      | 1               | 8                 |
| Gamma-glutamyltransferase increased    |                 |                   |
| subjects affected / exposed            | 0 / 13 (0.00%)  | 8 / 103 (7.77%)   |
| occurrences (all)                      | 0               | 12                |
| Lipase increased                       |                 |                   |
| subjects affected / exposed            | 1 / 13 (7.69%)  | 19 / 103 (18.45%) |
| occurrences (all)                      | 2               | 29                |
| Platelet count decreased               |                 |                   |
| subjects affected / exposed            | 1 / 13 (7.69%)  | 3 / 103 (2.91%)   |
| occurrences (all)                      | 1               | 3                 |
| Weight decreased                       |                 |                   |

|                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                  |                                                                                                                                           |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                    | 0 / 13 (0.00%)<br>0                                                                                                              | 14 / 103 (13.59%)<br>16                                                                                                                   |  |
| Congenital, familial and genetic disorders<br>Hypertrophic cardiomyopathy<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                       | 1 / 13 (7.69%)<br>1                                                                                                              | 0 / 103 (0.00%)<br>0                                                                                                                      |  |
| Cardiac disorders<br>Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                  | 1 / 13 (7.69%)<br>1                                                                                                              | 0 / 103 (0.00%)<br>0                                                                                                                      |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Tunnel vision<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0<br><br>1 / 13 (7.69%)<br>1<br><br>2 / 13 (15.38%)<br>3<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>2 | 10 / 103 (9.71%)<br>13<br><br>2 / 103 (1.94%)<br>2<br><br>16 / 103 (15.53%)<br>16<br><br>4 / 103 (3.88%)<br>5<br><br>0 / 103 (0.00%)<br>0 |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Lymphopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                   | 1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1                                                        | 1 / 103 (0.97%)<br>1<br><br>0 / 103 (0.00%)<br>0<br><br>10 / 103 (9.71%)<br>16                                                            |  |

|                                                 |                 |                   |  |
|-------------------------------------------------|-----------------|-------------------|--|
| Gastrointestinal disorders                      |                 |                   |  |
| Diarrhoea                                       |                 |                   |  |
| subjects affected / exposed                     | 7 / 13 (53.85%) | 41 / 103 (39.81%) |  |
| occurrences (all)                               | 7               | 60                |  |
| Anal haemorrhage                                |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 0 / 103 (0.00%)   |  |
| occurrences (all)                               | 2               | 0                 |  |
| Abdominal pain upper                            |                 |                   |  |
| subjects affected / exposed                     | 0 / 13 (0.00%)  | 6 / 103 (5.83%)   |  |
| occurrences (all)                               | 0               | 7                 |  |
| Constipation                                    |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 11 / 103 (10.68%) |  |
| occurrences (all)                               | 1               | 13                |  |
| Vomiting                                        |                 |                   |  |
| subjects affected / exposed                     | 2 / 13 (15.38%) | 18 / 103 (17.48%) |  |
| occurrences (all)                               | 2               | 25                |  |
| Nausea                                          |                 |                   |  |
| subjects affected / exposed                     | 2 / 13 (15.38%) | 29 / 103 (28.16%) |  |
| occurrences (all)                               | 2               | 44                |  |
| Skin and subcutaneous tissue disorders          |                 |                   |  |
| Pruritus                                        |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 5 / 103 (4.85%)   |  |
| occurrences (all)                               | 2               | 5                 |  |
| Rash                                            |                 |                   |  |
| subjects affected / exposed                     | 2 / 13 (15.38%) | 8 / 103 (7.77%)   |  |
| occurrences (all)                               | 2               | 19                |  |
| Rash pruritic                                   |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 2 / 103 (1.94%)   |  |
| occurrences (all)                               | 1               | 2                 |  |
| Skin exfoliation                                |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 0 / 103 (0.00%)   |  |
| occurrences (all)                               | 1               | 0                 |  |
| Musculoskeletal and connective tissue disorders |                 |                   |  |
| Arthralgia                                      |                 |                   |  |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 7 / 103 (6.80%)   |  |
| occurrences (all)                               | 1               | 8                 |  |

|                                    |                |                   |  |
|------------------------------------|----------------|-------------------|--|
| Back pain                          |                |                   |  |
| subjects affected / exposed        | 0 / 13 (0.00%) | 12 / 103 (11.65%) |  |
| occurrences (all)                  | 0              | 13                |  |
| Bone pain                          |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 2 / 103 (1.94%)   |  |
| occurrences (all)                  | 1              | 2                 |  |
| Musculoskeletal chest pain         |                |                   |  |
| subjects affected / exposed        | 0 / 13 (0.00%) | 6 / 103 (5.83%)   |  |
| occurrences (all)                  | 0              | 6                 |  |
| Myalgia                            |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 7 / 103 (6.80%)   |  |
| occurrences (all)                  | 1              | 11                |  |
| Pain in extremity                  |                |                   |  |
| subjects affected / exposed        | 0 / 13 (0.00%) | 13 / 103 (12.62%) |  |
| occurrences (all)                  | 0              | 14                |  |
| Infections and infestations        |                |                   |  |
| Localised infection                |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 0 / 103 (0.00%)   |  |
| occurrences (all)                  | 1              | 0                 |  |
| Pneumonia                          |                |                   |  |
| subjects affected / exposed        | 0 / 13 (0.00%) | 8 / 103 (7.77%)   |  |
| occurrences (all)                  | 0              | 9                 |  |
| Tonsillitis                        |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 0 / 103 (0.00%)   |  |
| occurrences (all)                  | 1              | 0                 |  |
| Metabolism and nutrition disorders |                |                   |  |
| Decreased appetite                 |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 11 / 103 (10.68%) |  |
| occurrences (all)                  | 2              | 12                |  |
| Hyperglycaemia                     |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 9 / 103 (8.74%)   |  |
| occurrences (all)                  | 2              | 14                |  |
| Hypertriglyceridaemia              |                |                   |  |
| subjects affected / exposed        | 1 / 13 (7.69%) | 3 / 103 (2.91%)   |  |
| occurrences (all)                  | 1              | 3                 |  |
| Hypoalbuminaemia                   |                |                   |  |



|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 3 / 103 (2.91%) |  |
| occurrences (all)           | 1              | 3               |  |
| Hypokalaemia                |                |                 |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 7 / 103 (6.80%) |  |
| occurrences (all)           | 0              | 7               |  |
| Hyponatraemia               |                |                 |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 7 / 103 (6.80%) |  |
| occurrences (all)           | 0              | 11              |  |
| Hypophosphataemia           |                |                 |  |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 103 (1.94%) |  |
| occurrences (all)           | 2              | 2               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                      |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 April 2019     | The following changes were as per amendment 02: 1. Updated primary objective of the study. 2. Corrected timing of AE assessments. 3. Revised Study Design. 4. Revised minimum age-related inclusion criterion.                 |
| 27 September 2019 | The primary reason for amendment 03 was to remove the interim analysis.                                                                                                                                                        |
| 24 September 2020 | The primary reason for amendment 04 was to maintain patient safety, confidentiality, and study integrity in the context of healthcare challenges presented by the coronavirus disease 2019 (COVID-19) public health emergency. |
| 12 February 2021  | The following changes were as per amendment 05: 1. Modified definition of end of study to include termination of study by sponsor. 2. Section added to provide posttrial access to brigatinib.                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported