



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	v1
This version publication date	26 June 2025
First version publication date	26 June 2025

Trial information

Trial identification

Sponsor protocol code	Brigatinib-2002
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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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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
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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
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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 Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	54.7 ± 11.94	-	
Gender categorical Units: Subjects			
Male	51	51	
Female	52	52	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	92	92	
Unknown or Not Reported	9	9	
Race 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 Units: centimetres (cm) arithmetic mean standard deviation	165.86 ± 10.172	-	
Weight Units: kilograms (kg) arithmetic mean	69.23		

standard deviation	± 15.409	-	
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End points

End points reporting groups

Reporting group title	Brigatinib 90 mg/180mg With Optional Dose Escalation to 240 mg
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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) ^[1]
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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 ≥ 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
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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.

End point values	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
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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 ≥ 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
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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	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	

End point values	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	

End point values	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
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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
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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	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
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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
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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	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
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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
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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	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
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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
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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	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
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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
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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	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)
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End point description:

OS is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. 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
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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	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)
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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
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End point timeframe:

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

End point values	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
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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
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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				
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
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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
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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, AEs are reported for 2 sets/arms. Arm 1 (brigatinib 90/180 mg) and Arm 2 (brigatinib 240 mg).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Brigatinib 240 mg
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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
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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	44	
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 %

Non-serious adverse events	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 occurrences (all)	0 / 13 (0.00%) 0	14 / 103 (13.59%) 16	
Congenital, familial and genetic disorders Hypertrophic cardiomyopathy subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 103 (0.00%) 0	
Cardiac disorders Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 103 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Tunnel vision subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 2 / 13 (15.38%) 3 1 / 13 (7.69%) 1 1 / 13 (7.69%) 2	10 / 103 (9.71%) 13 2 / 103 (1.94%) 2 16 / 103 (15.53%) 16 4 / 103 (3.88%) 5 0 / 103 (0.00%) 0	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1	1 / 103 (0.97%) 1 0 / 103 (0.00%) 0 10 / 103 (9.71%) 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 occurrences (all)	0 / 13 (0.00%) 0	12 / 103 (11.65%) 13	
Bone pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 103 (1.94%) 2	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	6 / 103 (5.83%) 6	
Myalgia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	7 / 103 (6.80%) 11	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	13 / 103 (12.62%) 14	
Infections and infestations Localised infection subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 103 (0.00%) 0	
Pneumonia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	8 / 103 (7.77%) 9	
Tonsillitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 103 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2	11 / 103 (10.68%) 12	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2	9 / 103 (8.74%) 14	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	3 / 103 (2.91%) 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported