Clinical trial results:
A Phase 3 Randomized Open-label Study of Brigatinib (ALUNBRIG®) Versus Alectinib (ALECENSA®) in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (XALKORI®)

Summary

EudraCT number	2018-001957-29
Trial protocol	FR SE ES DE AT GR HR IT RO
Global end of trial date	12 September 2024

Results information

Result version number	v1
This version publication date	14 February 2025
First version publication date	14 February 2025

Trial information

Trial identification

Sponsor protocol code	Brigatinib-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03596866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, 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	Interim
Date of interim/final analysis	12 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2024
Global end of trial reached?	Yes
Global end of trial date	12 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of Brigatinib to that of Alectinib in participants with anaplastic lymphoma kinase-positive (ALK+) locally advanced or metastatic non–small-cell lung cancer (NSCLC) who have progressed on Crizotinib as evidenced by PFS as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Protection of trial subjects:

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

Background therapy:

NA

Evidence for comparator: -

Actual start date of recruitment	19 April 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	Argentina: 2
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hong Kong: 11
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	China: 93
Worldwide total number of subjects	248
EEA total number of subjects	30

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)	205
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at various investigative sites globally.

Pre-assignment

Screening details:

Participants with ALK+ NSCLC who had progressed on crizotinib were administered either brigatinib or alectinib in this study. Data in this record is presented for primary results as the study was ongoing at data cut-off date (primary completion date). The data is reported for primary outcome measure up to primary completion date: 27 February 2024.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brigatinib

Arm description:

Participants were administered brigatinib 90 mg, tablets, orally, QD for 7 days, followed by brigatinib 180 mg, tablets, orally, QD until objective disease progression per RECIST v1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	AP26113
Other name	Alunbrig
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Brigatinib 90 mg, tablets, orally, QD for 7 days was administered to participants followed by brigatinib 180 mg, tablets, orally, QD until objective disease progression per RECIST v1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Arm title	Alectinib

Arm description:

Participants were administered alectinib 600 mg, capsules, orally, BID until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Arm type	Active comparator
Investigational medicinal product name	Alectinib
Investigational medicinal product code	RO5424802/F03
Other name	Alecensa
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Alectinib 600 mg, capsules, orally was administered to participants BID until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Number of subjects in period 1	Brigatinib	Alectinib
Started	125	123
Completed	0	0
Not completed	125	123
Adverse event, serious fatal	27	14
Consent withdrawn by subject	6	5
Ongoing at Data Cut-off	91	101
Reason Not Specified	-	1
Randomized but Never Received Drug	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Brigatinib
Reporting group description:	
Participants were administered brigatinib 90 mg, tablets, orally, QD for 7 days, followed by brigatinib 180 mg, tablets, orally, QD until objective disease progression per RECIST v1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.	
Reporting group title	Alectinib
Reporting group description:	
Participants were administered alectinib 600 mg, capsules, orally, BID until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.	

Reporting group values	Brigatinib	Alectinib	Total
Number of subjects	125	123	248
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.0	52.9	
standard deviation	± 12.17	± 13.53	-
Gender categorical Units: Subjects			
Female	67	68	135
Male	58	55	113
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	14	21
Not Hispanic or Latino	116	106	222
Unknown or Not Reported	2	3	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	74	66	140
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	2
White	50	52	102
More than one race	0	0	0
Unknown or Not Reported	1	3	4

End points

End points reporting groups

Reporting group title	Brigatinib
Reporting group description:	
Participants were administered brigatinib 90 mg, tablets, orally, QD for 7 days, followed by brigatinib 180 mg, tablets, orally, QD until objective disease progression per RECIST v1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.	
Reporting group title	Alectinib
Reporting group description:	
Participants were administered alectinib 600 mg, capsules, orally, BID until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.	

Primary: Progression-free Survival (PFS) as Assessed by Blinded Independent Review Committee (BIRC) per RECIST v1.1

End point title	Progression-free Survival (PFS) as Assessed by Blinded Independent Review Committee (BIRC) per RECIST v1.1
End point description:	
PFS is defined as the time interval from the date of randomization until the first date at which disease progression is objectively documented via RECIST v1.1 by BIRC, or death due to any cause, whichever occurs first, in the full analysis set. PFS will be censored for participants without documented disease progression or death at the last valid tumor response assessment. FAS included all participants randomized to each regimen regardless of whether they were ALK+ by an FDA approved test (Vysis ALK Break Apart FISH Probe Kit, Ventana ALK (D5F3) CDx Assay, Foundation Medicine's FoundationOne CDx) or a local test other than FISH and immunohistochemistry, or whether they received study drug or adhered to the assigned dose. '99999' indicates that the upper limit of 95% confidence interval (CI) was not estimable due to censoring.	
End point type	Primary
End point timeframe:	
Up to 33.8 months	

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	123		
Units: months				
median (confidence interval 95%)	19.253 (15.671 to 99999)	19.187 (12.879 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Brigatinib v Alectinib

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8672 [1]
Method	2-sided Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.968
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.658
upper limit	1.424

Notes:

[1] - P-value from a 2-sided stratified log-rank test using the stratification factors: presence of intracranial central nervous system (CNS) metastases at baseline, and best prior response to crizotinib therapy as assessed by the investigator.

Secondary: Intracranial Objective Response Rate (iORR) as Assessed by BIRC per Modified RECIST v1.1

End point title	Intracranial Objective Response Rate (iORR) as Assessed by BIRC per Modified RECIST v1.1

End point description:

iORR, as assessed by the BIRC, is defined as the percentage of the participants who have achieved CR or PR in the central nervous system (CNS) per a modification RECIST v1.1 after the initiation of study treatment in participants with CNS metastases at baseline. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of participants				
number (not applicable)				

Notes:

[2] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[3] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQOL) from European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 v3.0) Score

End point title	Health-Related Quality of Life (HRQOL) from European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 v3.0) 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 and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). It 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 0-100. For the functional scales & global health status scale, higher scores represent better quality of life (QOL); for symptom scales, lower scores represent better QOL. Data in this record are presented for primary results as study was ongoing at data cut-off date (primary completion date). Number of subjects analysed is zero as analysis of this endpoint was ongoing at data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[5] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: HRQOL from EORTC QLQ- Lung Cancer (LC) 13

End point title	HRQOL from EORTC QLQ- Lung Cancer (LC) 13

End point description:

HRQOL scores will be assessed with European Organization for Research and Treatment (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. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[7] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Intracranial Disease Progression (iPD) as Assessed by BIRC per Modified RECIST v1.1

End point title	Time to Intracranial Disease Progression (iPD) as Assessed by BIRC per Modified RECIST v1.1

End point description:

Time to iPD, as assessed by the BIRC, is defined as the time interval from the date of randomization until the first date at which iPD is objectively documented via a modification of RECIST v1.1. Time to iPD will be censored for participants without documented iPD at the last valid intracranial tumor response assessment. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[8] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[9] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by Investigator per RECIST v1.1

End point title	PFS as Assessed by Investigator per RECIST v1.1

End point description:

PFS is defined as the time interval from the date of randomization until the first date at which disease progression is objectively documented via RECIST v1.1 by investigator, or death due to any cause, whichever occurs first, in the full analysis set. PFS will be censored for participants without documented disease progression or death at the last valid tumor response assessment. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[10] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[11] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by Investigator and BIRC Per RECIST v1.1

End point title	Duration of Response (DOR) as Assessed by Investigator and BIRC Per RECIST v1.1

End point description:

DOR is defined as the time interval from the time that the measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that the progressive disease (PD) is objectively documented or death, as assessed by the investigator and BIRC, using RECIST v1.1. For the responders who have not progressed or died, they will be censored at the last tumor assessment date prior to receiving subsequent anticancer therapy. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[12] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[13] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response as Assessed by Investigator and BIRC Per RECIST v1.1

End point title	Time to Response as Assessed by Investigator and BIRC Per RECIST v1.1

End point description:

Time to response is defined as the time interval from randomization until the initial observation of CR or PR, as assessed by the investigator and BIRC, using RECIST v1.1. Time to response will be summarized using descriptive statistics in participants with confirmed objective response. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[14] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[15] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Duration of Response (iDOR) as Assessed by the BIRC per Modified RECIST v1.1

End point title	Intracranial Duration of Response (iDOR) as Assessed by the BIRC per Modified RECIST v1.1

End point description:

iDOR, as assessed by the BIRC per modified RECIST v1.1, is defined as the time interval from the time that the measurement criteria are first met for CR or PR in the CNS (whichever is first recorded) until the first date that the PD in the CNS is objectively documented or death. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[16] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[17] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as Assessed by Investigator and BIRC per RECIST v1.1

End point title	Objective Response Rate (ORR) as Assessed by Investigator and BIRC per RECIST v1.1

End point description:

ORR is defined as the percentage of the participants who are confirmed to have achieved complete response (CR) or partial response (PR), using RECIST v1.1 after the initiation of study treatment. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: percentage of participants				
number (not applicable)				

Notes:

[18] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[19] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

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 randomization until death due to any cause in the full analysis set. It will be censored on the date of last contact for those participants who are alive. Data in this record are presented for primary results as the study was ongoing at the data cut-off date (primary completion date). The number of subjects analysed is zero as the analysis of this endpoint was ongoing at the data cut-off date of 27 February 2024.

End point type	Secondary

End point timeframe:

5 years

End point values	Brigatinib	Alectinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[20] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

[21] - The analysis was ongoing at the data cut-off date and will be reported during final results posting.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 33.8 months

Adverse event reporting additional description:

Safety Analysis Set included all participants who received at least 1 dose of study drug. As per planned analysis, data for adverse events was collected per treatment groups (brigatinib and alectinib) irrespective of the dosing regimen and is presented accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Brigatinib

Reporting group description:

Participants were administered brigatinib 90 mg, tablets, orally, QD for 7 days, followed by brigatinib 180 mg, tablets, orally, QD until objective disease progression per RECIST v1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Reporting group title	Alectinib

Reporting group description:

Participants were administered alectinib 600 mg, capsules, orally, BID until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity, or up to 33.8 months.

Serious adverse events	Brigatinib	Alectinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 125 (30.40%)	24 / 122 (19.67%)	
number of deaths (all causes)	37	25	
number of deaths resulting from adverse events	12	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			

subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma	Additional description: Number of participants at risk in each arm is based on the male population in this study.		
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma recurrent			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	3 / 125 (2.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic mass			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 125 (2.40%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 125 (4.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	5 / 125 (4.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 125 (1.60%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Cardiovascular somatic symptom disorder			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 125 (0.80%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchoscopy			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
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			
Radiation necrosis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 125 (0.80%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 125 (0.80%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain lower			
subjects affected / exposed	1 / 125 (0.80%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash maculo-papular			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
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 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 125 (1.60%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 125 (1.60%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 125 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 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	Alectinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 125 (97.60%)	118 / 122 (96.72%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	59 / 125 (47.20%)	47 / 122 (38.52%)	
occurrences (all)	112	103	
Alpha hydroxybutyrate dehydrogenase increased			
subjects affected / exposed	8 / 125 (6.40%)	0 / 122 (0.00%)	
occurrences (all)	18	0	
Amylase increased			

subjects affected / exposed	26 / 125 (20.80%)	14 / 122 (11.48%)	
occurrences (all)	62	36	
Aspartate aminotransferase increased			
subjects affected / exposed	71 / 125 (56.80%)	51 / 122 (41.80%)	
occurrences (all)	177	127	
Blood bilirubin increased			
subjects affected / exposed	7 / 125 (5.60%)	39 / 122 (31.97%)	
occurrences (all)	9	121	
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 125 (12.80%)	25 / 122 (20.49%)	
occurrences (all)	26	49	
Bilirubin conjugated increased			
subjects affected / exposed	2 / 125 (1.60%)	10 / 122 (8.20%)	
occurrences (all)	3	21	
Blood bilirubin unconjugated increased			
subjects affected / exposed	2 / 125 (1.60%)	7 / 122 (5.74%)	
occurrences (all)	3	18	
Blood insulin increased			
subjects affected / exposed	14 / 125 (11.20%)	9 / 122 (7.38%)	
occurrences (all)	35	12	
Blood glucose increased			
subjects affected / exposed	9 / 125 (7.20%)	3 / 122 (2.46%)	
occurrences (all)	17	6	
Blood creatinine increased			
subjects affected / exposed	16 / 125 (12.80%)	21 / 122 (17.21%)	
occurrences (all)	42	68	
Blood creatine phosphokinase increased			
subjects affected / exposed	92 / 125 (73.60%)	39 / 122 (31.97%)	
occurrences (all)	279	102	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	7 / 125 (5.60%)	3 / 122 (2.46%)	
occurrences (all)	22	3	
Blood cholesterol increased			

subjects affected / exposed	8 / 125 (6.40%)	3 / 122 (2.46%)	
occurrences (all)	14	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	25 / 125 (20.00%)	13 / 122 (10.66%)	
occurrences (all)	46	43	
Lipase increased			
subjects affected / exposed	29 / 125 (23.20%)	23 / 122 (18.85%)	
occurrences (all)	78	66	
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 125 (6.40%)	2 / 122 (1.64%)	
occurrences (all)	17	2	
Blood urea increased			
subjects affected / exposed	1 / 125 (0.80%)	9 / 122 (7.38%)	
occurrences (all)	1	15	
White blood cell count decreased			
subjects affected / exposed	1 / 125 (0.80%)	7 / 122 (5.74%)	
occurrences (all)	3	14	
Weight increased			
subjects affected / exposed	6 / 125 (4.80%)	12 / 122 (9.84%)	
occurrences (all)	6	18	
Weight decreased			
subjects affected / exposed	11 / 125 (8.80%)	3 / 122 (2.46%)	
occurrences (all)	22	7	
Neutrophil count decreased			
subjects affected / exposed	3 / 125 (2.40%)	7 / 122 (5.74%)	
occurrences (all)	4	17	
Vascular disorders			
Hypertension			
subjects affected / exposed	38 / 125 (30.40%)	5 / 122 (4.10%)	
occurrences (all)	63	7	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 125 (18.40%)	21 / 122 (17.21%)	
occurrences (all)	38	29	
Dizziness			

subjects affected / exposed	10 / 125 (8.00%)	8 / 122 (6.56%)	
occurrences (all)	11	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 125 (21.60%)	45 / 122 (36.89%)	
occurrences (all)	58	136	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 125 (8.80%)	19 / 122 (15.57%)	
occurrences (all)	16	26	
Influenza like illness			
subjects affected / exposed	9 / 125 (7.20%)	9 / 122 (7.38%)	
occurrences (all)	12	12	
Asthenia			
subjects affected / exposed	15 / 125 (12.00%)	8 / 122 (6.56%)	
occurrences (all)	19	10	
Oedema peripheral			
subjects affected / exposed	4 / 125 (3.20%)	23 / 122 (18.85%)	
occurrences (all)	5	27	
Pyrexia			
subjects affected / exposed	4 / 125 (3.20%)	7 / 122 (5.74%)	
occurrences (all)	8	13	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 125 (4.80%)	7 / 122 (5.74%)	
occurrences (all)	7	8	
Constipation			
subjects affected / exposed	14 / 125 (11.20%)	35 / 122 (28.69%)	
occurrences (all)	17	52	
Nausea			
subjects affected / exposed	18 / 125 (14.40%)	11 / 122 (9.02%)	
occurrences (all)	29	38	
Vomiting			
subjects affected / exposed	13 / 125 (10.40%)	12 / 122 (9.84%)	
occurrences (all)	115	17	
Diarrhoea			

subjects affected / exposed	16 / 125 (12.80%)	21 / 122 (17.21%)	
occurrences (all)	19	32	
Dyspepsia			
subjects affected / exposed	7 / 125 (5.60%)	2 / 122 (1.64%)	
occurrences (all)	11	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 125 (12.80%)	26 / 122 (21.31%)	
occurrences (all)	18	33	
Productive cough			
subjects affected / exposed	3 / 125 (2.40%)	8 / 122 (6.56%)	
occurrences (all)	3	11	
Dyspnoea			
subjects affected / exposed	15 / 125 (12.00%)	12 / 122 (9.84%)	
occurrences (all)	18	13	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	8 / 125 (6.40%)	2 / 122 (1.64%)	
occurrences (all)	18	4	
Pruritus			
subjects affected / exposed	9 / 125 (7.20%)	11 / 122 (9.02%)	
occurrences (all)	11	12	
Rash			
subjects affected / exposed	19 / 125 (15.20%)	12 / 122 (9.84%)	
occurrences (all)	31	15	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 125 (5.60%)	6 / 122 (4.92%)	
occurrences (all)	7	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 125 (12.00%)	19 / 122 (15.57%)	
occurrences (all)	25	31	
Back pain			
subjects affected / exposed	13 / 125 (10.40%)	16 / 122 (13.11%)	
occurrences (all)	17	20	

Pain in extremity			
subjects affected / exposed	8 / 125 (6.40%)	6 / 122 (4.92%)	
occurrences (all)	11	7	
Myalgia			
subjects affected / exposed	8 / 125 (6.40%)	20 / 122 (16.39%)	
occurrences (all)	14	27	
Muscle spasms			
subjects affected / exposed	7 / 125 (5.60%)	3 / 122 (2.46%)	
occurrences (all)	10	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 125 (3.20%)	8 / 122 (6.56%)	
occurrences (all)	6	11	
Nasopharyngitis			
subjects affected / exposed	3 / 125 (2.40%)	7 / 122 (5.74%)	
occurrences (all)	4	7	
COVID-19			
subjects affected / exposed	13 / 125 (10.40%)	13 / 122 (10.66%)	
occurrences (all)	15	13	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	12 / 125 (9.60%)	17 / 122 (13.93%)	
occurrences (all)	31	56	
Hypercholesterolaemia			
subjects affected / exposed	8 / 125 (6.40%)	2 / 122 (1.64%)	
occurrences (all)	13	4	
Hyperglycaemia			
subjects affected / exposed	13 / 125 (10.40%)	11 / 122 (9.02%)	
occurrences (all)	22	28	
Hypertriglyceridaemia			
subjects affected / exposed	9 / 125 (7.20%)	5 / 122 (4.10%)	
occurrences (all)	20	12	
Decreased appetite			
subjects affected / exposed	16 / 125 (12.80%)	5 / 122 (4.10%)	
occurrences (all)	17	9	
Hyponatraemia			

subjects affected / exposed	10 / 125 (8.00%)	8 / 122 (6.56%)	
occurrences (all)	22	18	
Hypokalaemia			
subjects affected / exposed	8 / 125 (6.40%)	12 / 122 (9.84%)	
occurrences (all)	22	16	
Hypoalbuminaemia			
subjects affected / exposed	7 / 125 (5.60%)	7 / 122 (5.74%)	
occurrences (all)	11	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2019	The following changes were made as per Amendment 2: 1. Updated Title to reflect Brigatinib (Alunbrig®) registration. 2. Updated the date that participant enrolment began. 3. Updated the guidance regarding female contraception. 4. Updated Excluded Medications to include moderate cytochrome P450 (CYP)3A inhibitors and to provide further guidance to investigators. 5. Updated inclusion criteria.
09 March 2020	The following changes were made as per Amendment 3: 1. Updated sponsor information from ARIAD Pharmaceuticals, Inc to Takeda Development Center Americas, Inc. 2. Removed "time to iPD" from the key secondary endpoints and revised the order of other secondary endpoints. 3. Added new exclusion criterion 7 (other primary malignancies other than NSCLC) and renumbered subsequent criteria. 4. Added requirement for acknowledgment of receipt when reporting adverse events (AEs) and serious adverse events (SAEs) by facsimile. 5. Revised the secondary endpoint analyses to reflect that iPD will no longer be a key secondary endpoint and was removed from hierarchical testing.
08 March 2021	The following changes were made as per Amendment 4: 1. Updated the creatine phosphokinase (CPK) dose modification guidance. 2. Updated the storage condition of Brigatinib to "Store at controlled room temperature of 20°C to 25°C with excursions permitted between 15°C to 30°C." 3. Added the description of direct-to-patient (DTP) drug delivery during the coronavirus disease 2019 (COVID-19) pandemic. 4. Added criteria to terminate BIRC assessment if the primary endpoint is met at the interim analysis (IA) or primary analysis, or not met at the primary analysis. 5. Added description of remote source document verification during the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported