Clinical trial results:
A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Participants with ALK-positive Advanced Lung Cancer

Summary

EudraCT number	2015-003447-19
Trial protocol	GB AT DE NL FI SE NO DK ES CZ PT FR IT
Global end of trial date	29 January 2021

Results information

Result version number	v1 (current)
This version publication date	12 August 2021
First version publication date	12 August 2021

Trial information

Trial identification

Sponsor protocol code	AP26113-13-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02737501
WHO universal trial number (UTN)	U1111-1210-4363

Notes:

Sponsors

Sponsor organisation name	ARIAD Pharmaceuticals
Sponsor organisation address	40 Lansdowne Street, Cambridge, MA, United States, 02139
Public contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to compare the efficacy of brigatinib to that of crizotinib in anaplastic lymphoma kinase (ALK) plus locally advanced or metastatic non–small-cell lung cancer (NSCLC) participants naive to ALK inhibitors, as evidenced by PFS.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2016
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	Australia: 7
Country: Number of subjects enrolled	Hong Kong: 16
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Luxembourg: 1
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	275
EEA total number of subjects	124

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)	188
From 65 to 84 years	84
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 92 investigative sites in Australia, Hong Kong, Singapore, South Korea, Taiwan, Austria, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom, Canada, and the United States of America from 26 May 2016 to 29 January 2021.

Pre-assignment

Screening details:

ALK+NSCLC participants who had not received ALK-targeted tyrosine kinase inhibitor(TKI)enrolled(1:1ratio) to receive brigatinib 90mg for 7 days followed by180mg or crizotinib250mg.Crizotinib arm participants with progressive disease(PD) or received radiotherapy to brain(Randomized Phase) were crossed over to brigatinib90mg/180mg(Crossover Phase).

Period 1

Period 1 title	Randomized Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomized Phase: Brigatinib 90 mg QD/180 QD

Arm description:

Brigatinib 90 mg, tablets, orally, once daily (QD) for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until disease progression (PD), intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets

Arm title	Randomized Phase: Crizotinib 250 mg BID

Arm description:

Crizotinib 250 mg, tablets, twice daily (BID) in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months).

Arm type	Active comparator
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Crizotinib tablets

Number of subjects in period 1	Randomized Phase: Brigatinib 90 mg QD/180 QD	Randomized Phase: Crizotinib 250 mg BID
Started	137	138
Safety Analysis Set	136	137
Completed	20	84
Not completed	117	54
Consent withdrawn by subject	16	6
Never Treated	1	1
Site Terminated by Sponsor	58	16
Died	41	29
Lost to follow-up	-	1
Reason not Specified	1	1

Period 2

Period 2 title	Crossover Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Crossover Phase: Brigatinib 90 mg QD/180 mg QD

Arm description:

Participants who experienced PD as assessed by the blinded Independent Review Committee (BIRC) or received radiotherapy to the brain while on 'Crizotinib 250 mg BID' therapy in Randomized Phase were crossed over. Following 10-day washout period, crossover participants received brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, tablets, orally, QD in each 28-day cycle up to end of the study (The median duration of exposure was 17.25 months).

Arm type	Experimental
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brigatinib tablets

Number of subjects in period 2[1]	Crossover Phase: Brigatinib 90 mg QD/180 mg QD
Started	65
Completed	10
Not completed	55
Withdrew Consent	9
Physician decision	1
Site Terminated by Sponsor	23
Died	22

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participants from crizotinib arm who experienced progressive disease (PD) or received radiotherapy to the brain in Randomized Phase crossed over to brigatinib in the Crossover Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Randomized Phase: Brigatinib 90 mg QD/180 QD
Reporting group description:	
Brigatinib 90 mg, tablets, orally, once daily (QD) for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until disease progression (PD), intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months).	
Reporting group title	Randomized Phase: Crizotinib 250 mg BID
Reporting group description:	
Crizotinib 250 mg, tablets, twice daily (BID) in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months).	

Reporting group values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Randomized Phase: Crizotinib 250 mg BID	Total
Number of subjects	137	138	275
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	93	95	188
From 65-84 years	42	42	84
85 years and over	2	1	3
Age Continuous Units: years			
arithmetic mean	57.9	58.6	
standard deviation	± 13.46	± 11.42	-
Sex: Female, Male Units: participants			
Female	69	81	150
Male	68	57	125
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	59	49	108
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	2
White	76	86	162
More than one race	0	0	0
Unknown or Not Reported	2	1	3
Race/Ethnicity, Customized Units: Subjects			
Hispanic, Latino or Spanish	6	10	16
Not Hispanic, Latino or Spanish	131	128	259

Region of Enrollment Units: Subjects			
Australia	2	5	7
Hong Kong	10	6	16
Singapore	5	1	6
Korea, Republic Of	29	28	57
Taiwan, Province Of China	12	9	21
Austria	5	4	9
Denmark	2	1	3
France	7	4	11
Germany	6	11	17
Italy	19	19	38
Luxembourg	1	0	1
Netherlands	5	6	11
Norway	0	2	2
Spain	14	17	31
Sweden	0	1	1
Switzerland	0	1	1
United Kingdom	10	8	18
Canada	0	2	2
United States	10	13	23
Global Health Status/Quality of Life (QoL)			
HRQoL:perceived quality of participant's life, includes self-reported multidimensional measures of physical, mental health.EORTC-QLQ-C30 contains 30 items across 5 functional scales(physical,role,cognitive,emotional,social),9 symptom scales(fatigue,nausea and vomiting,pain,dyspnea,sleep disturbance,appetite loss,constipation,diarrhea,financial difficulties),a global health status/QOL scale on 4 response levels(not at all,a little,quite a bit,very much),with 2 questions relying on a 7-point numeric rating scale.Raw scores converted into overall score of 0-100,lower scores			
Units: score on a scale arithmetic mean full range (min-max)			-

Subject analysis sets

Subject analysis set title	Randomized Phase: Brigatinib 90 mg QD/180 QD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until PD, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months). Intent-to-treat (ITT) Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Number analyzed is number of participants with data available for global health status/QoL at Baseline.

Subject analysis set title	Randomized Phase: Crizotinib 250 mg BID
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crizotinib 250 mg, tablets, BID in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months). Intent-to-treat (ITT) Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Number analyzed is number of participants with data available for global health status/QoL at Baseline.

Reporting group values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Randomized Phase: Crizotinib 250 mg BID	
Number of subjects	131	131	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	±	±	
Sex: Female, Male Units: participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Race/Ethnicity, Customized Units: Subjects			
Hispanic, Latino or Spanish Not Hispanic, Latino or Spanish			
Region of Enrollment Units: Subjects			
Australia Hong Kong Singapore Korea, Republic Of Taiwan, Province Of China Austria Denmark France Germany Italy Luxembourg Netherlands			

Norway Spain Sweden Switzerland United Kingdom Canada United States			
Global Health Status/Quality of Life (QoL)			
HRQoL:perceived quality of participant’s life, includes self-reported multidimensional measures of physical, mental health.EORTC-QLQ-C30 contains 30 items across 5 functional scales(physical,role,cognitive,emotional,social),9 symptom scales(fatigue,nausea and vomiting,pain,dyspnea,sleep disturbance,appetite loss,constipation,diarrhea,financial difficulties),a global health status/QOL scale on 4 response levels(not at all,a little,quite a bit,very much),with 2 questions relying on a 7-point numeric rating scale.Raw scores converted into overall score of 0-100,lower scores			
Units: score on a scale arithmetic mean full range (min-max)	 60.432 0.00 to 100.00	 59.160 0.00 to 100.00	

End points

End points reporting groups

Reporting group title	Randomized Phase: Brigatinib 90 mg QD/180 QD

Reporting group description:

Brigatinib 90 mg, tablets, orally, once daily (QD) for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until disease progression (PD), intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months).

Reporting group title	Randomized Phase: Crizotinib 250 mg BID

Reporting group description:

Crizotinib 250 mg, tablets, twice daily (BID) in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months).

Reporting group title	Crossover Phase: Brigatinib 90 mg QD/180 mg QD

Reporting group description:

Participants who experienced PD as assessed by the blinded Independent Review Committee (BIRC) or received radiotherapy to the brain while on 'Crizotinib 250 mg BID' therapy in Randomized Phase were crossed over. Following 10-day washout period, crossover participants received brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, tablets, orally, QD in each 28-day cycle up to end of the study (The median duration of exposure was 17.25 months).

Subject analysis set title	Randomized Phase: Brigatinib 90 mg QD/180 QD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until PD, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months). Intent-to-treat (ITT) Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Number analyzed is number of participants with data available for global health status/QoL at Baseline.

Subject analysis set title	Randomized Phase: Crizotinib 250 mg BID
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crizotinib 250 mg, tablets, BID in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months). Intent-to-treat (ITT) Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Number analyzed is number of participants with data available for global health status/QoL at Baseline.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS as assessed by Blinded Independent Review Committee (BIRC), per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, was defined as the time interval from the date of randomization until the date of the PFS event. The data was censored for participants without a PFS event. ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose.

End point type	Primary

End point timeframe:

Up to end of study (Up to 56 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	65	138	
Units: months				
median (confidence interval 95%)	24.016 (18.46 to 43.20)	16.821 (10.12 to 23.85)	11.072 (9.13 to 13.01)	

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.481
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.66

Notes:

[1] - The hazard ratio was obtained using a Cox proportional hazards model with randomization stratification factors
(current) as covariates.
[2] - P-values are from a log-rank test stratified by randomization stratification factors (current; presence of intracranial central nervous system (iCNS) metastases at baseline and prior chemotherapy for locally advanced or metastatic disease).

Secondary: Confirmed Objective Response Rate (ORR)

End point title	Confirmed Objective Response Rate (ORR)

End point description:

ORR was defined as percentage of participants who achieved Complete response (CR) or Partial responses (PR) using Response Evaluation Criteria in Solid Tumors (RECIST) version (v). 1.1 criteria. CR is defined as disappearance of all extranodal target and non-target lesions. All pathological lymph nodes must have decreased to less than (<) 10 mm in short axis for target lesions and all lymph nodes must be non-pathological in size (<10 mm short axis), normalization of tumor marker level for non-target lesions. PR is at least a 30% decrease in SLD of target lesions, taking as reference baseline sum diameters. ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (Up to 36 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	65	138	
Units: percentage of participants				
number (confidence interval 95%)	74.5 (66.30 to 81.52)	56.9 (44.04 to 69.15)	62.3 (53.68 to 70.42)	

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.033
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.91

Notes:

[3] - Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by presence of intracranial central nervous system (iCNS) metastases at Baseline, and prior chemotherapy for locally advanced or metastatic disease (current strata).

Secondary: Confirmed Intracranial ORR (iORR)

End point title	Confirmed Intracranial ORR (iORR)

End point description:

ORR was defined as percentage of participants who achieved CR or PR in the central nervous system (CNS) in randomized participants with intracranial CNS metastasis at baseline. CR is defined as disappearance of all extranodal target and non-target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis for target lesions and all lymph nodes must be non-pathological in size (<10 mm short axis), normalization of tumor marker level for non-target lesions. PR is at least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters. ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Overall number of participants analyzed are the participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (Up to 36 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	42	49	
Units: percentage of participants				
number (confidence interval 95%)	66.0 (50.69 to 79.14)	35.7 (21.55 to 51.97)	14.3 (5.94 to 27.24)	

Statistical analyses

Statistical analysis title	Statistical Analysis for iORR
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	13.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	39.11

Notes:

[4] - Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by presence of prior chemotherapy for Locally advanced or metastatic disease at study entry (current strata).

Secondary: Intracranial Progression Free Survival

End point title	Intracranial Progression Free Survival

End point description:

Intracranial PFS as assessed by BIRC, is defined as the time from randomization until first CNS PD is documented, or death due to any cause. PD is SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest), the SLD must also demonstrate an absolute increase of at least 5 mm, and unequivocal progression of existing non-target lesions. ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Overall number of participants analyzed are the participants with data available for analyses. 99999 indicates upper limit of 95% confidence interval (CI) was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Baseline up to end of study (Up to 56 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	42	49	
Units: months				
median (confidence interval 95%)	23.951 (12.91 to 30.78)	24.542 (12.58 to 99999)	5.520 (3.71 to 7.52)	

Statistical analyses

Statistical analysis title	Statistical Analysis for Intracranial PFS
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.51

Notes:

[5] - The hazard ratio was obtained using a Cox proportional hazards model with prior chemotherapy for locally advanced or metastatic disease (current strata) as covariate.

[6] - P-values are from a log-rank test stratified by randomization stratification factors (current; presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease).

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time from randomization until death due to any cause.ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. 99999 indicates that median and 95% CI was not estimable due to fewer number of participants with events. 999999 indicates upper limit of 95% CI was not estimable due to fewer number of participants with events.

End point type	Secondary

End point timeframe:

Baseline up to end of study (Up to 56 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	65	138	
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	35.023 (30.42 to 999999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR as assessed by BIRC:time interval from date that criteria are first met for CR/PR(whichever is first recorded)until first date that progressive disease(PD)is objectively documented.CR:disappearance of all extranodal target and non-target lesions.All pathological lymph nodes must have decreased to<10mm in short axis for target lesions,all lymph nodes must be non-pathological in size(<10mm short axis),normalization of tumor marker level for non-target lesions.PR:>=30%decrease in SLD of target lesions,taking as reference baseline sum diameters.PD:SLD increased by>=20%from smallest value on study(including baseline,if that is smallest),SLD must also demonstrate absolute increase of>=5mm,for non-target lesions,unequivocal progression of existing non-target lesions.ITT Population:all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to assigned dose.Only responders were reported for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to end of study (Up to 56 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	37	86	
Units: months				
median (full range (min-max))	33.150 (1.84 to 50.60)	19.154 (1.97 to 33.15)	13.832 (1.45 to 49.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

Time to response as assessed by BIRC, assessment and is defined as the time interval from the date of randomization until the initial observation of CR or PR. CR is defined as disappearance of all extranodal target and non-target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis for target lesions and all lymph nodes must be non-pathological in size (<10 mm short axis), normalization of tumor marker level for non-target lesions. PR is at least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters. ITT Population included all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to the assigned dose. Only responders were reported for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (Up to 36 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	65	138	
Units: months				
median (full range (min-max))	1.840 (1.02 to 29.47)	1.873 (0.20 to 18.33)	1.873 (0.79 to 7.43)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control as assessed by BIRC:percentage of randomized participants who have achieved CR,PR,or stable disease(SD)after randomization.CR:disappearance of all extranodal target and non-target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis for target lesions and all lymph nodes must be non-pathological in size (<10 mm short axis), normalization of tumor marker level for non-target lesions. PR: >=30% decrease in SLD of target lesions, taking as reference baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD:SLD increased by >=20% from the smallest value on study, SLD must also demonstrate an absolute increase of >=5 mm, and unequivocal progression of existing non-target lesions. ITT Population:all participants randomized to each regimen regardless of whether they tested ALK+, or whether they received study drug or adhered to assigned dose.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (Up to 36 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	65	138	
Units: percentage of participants				
number (confidence interval 95%)	85.4 (78.36 to 90.85)	73.8 (61.46 to 83.97)	86.2 (79.34 to 91.50)	

Statistical analyses

Statistical analysis title	Statistical Analysis for DCR
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.822
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.82

Notes:

[7] - Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by presence of iCNS metastases at Baseline, and prior chemotherapy for locally advanced or metastatic disease (current strata).

Secondary: Percentage of Participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participants with Treatment-emergent Adverse Events (TEAEs)

End point description:

An AE is any untoward medical occurrence in a participant. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition which is temporally associated with the use of the study drug (i.e., occurs after the first dose of study drug) is also an AE. TEAEs are defined as AEs starting/worsening on or after the first dose of study treatment and no later than the earliest of 30 days after the last dose of the treatment to which the participant was assigned, or the day before start of brigatinib therapy in crossover participant. Treated Population included all participant who received ≥at least 1 dose of study drug and served as basis of safety analysis.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after last dose of study drug (Up to approximately 37 months)

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136	65	137	
Units: percentage of participants				
number (not applicable)	100	98.5	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Global Health Status/Quality of Life as Assessed by EORTC QLQ-C30 (Version 3.0)

End point title	Change from Baseline in Global Health Status/Quality of Life as Assessed by EORTC QLQ-C30 (Version 3.0)

End point description:

HRQoL:perceived quality of participant’s life,includes self-reported multidimensional measures of physical,mental health.Patient-reported symptoms(PROs)and HRQoL-collected by administering european organisation for research and treatment of cancer(EORTC)quality of life(QLQ)-C30questionnaire,which contains 30 items across 5 functional scales(physical,role,cognitive,emotional,social),9 symptom scales(fatigue,nausea and vomiting,pain,dyspnea,sleep disturbance,appetite loss,constipation,diarrhea,financial difficulties),global health status/QOL scale.30 items have 4 response levels(not at all,a little,quite a bit,very much),2 questions rely on7-point numeric rating scale.Raw scores converted into overall score of 0-100,where lower scores=better QOL.A negative change from Baseline=improvement.ITT Population:all participants randomized regardless of ALK+ status/received study drug/adhered to assigned dose.Overall number of participants analyzed:participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Month 36

End point values	Randomized Phase: Brigatinib 90 mg QD/180 QD	Randomized Phase: Crizotinib 250 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	53		
Units: score on a scale				
arithmetic mean (standard deviation)	4.007 (± 25.7563)	-4.088 (± 27.4748)		

Statistical analyses

Statistical analysis title	Statistical Analysis for HRQoL
Comparison groups	Randomized Phase: Brigatinib 90 mg QD/180 QD v Randomized Phase: Crizotinib 250 mg BID

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0295 [9]
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	5.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	11

Notes:

[8] - A mixed effect model is used with an unstructured covariance matrix.

[9] - p-values were obtained using mixed effects models stratified by presence of iCNS metastases at study entry, prior chemotherapy at Baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality - Up to 56 months; Serious and other adverse events - From first dose up to 30 days after last dose of study drug (Up to approximately 37 months)

Adverse event reporting additional description:

All Cause-mortality:ITT Population[participants randomized regardless of-ALK+status/received study drug/took assigned dose:N=137,138,65].Serious+other(Nonserious):Treated Population(participants who had≥1dose,included in safety analysis).Crossover Population:'Crizotinib 250mgBID'participants who crossed over to brigatinib after BIRC-assessed PD.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Randomized Phase: Brigatinib 90 mg QD/180 QD

Reporting group description:

Brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, orally, QD, in each 28-day cycle until PD, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 34.86 months).

Reporting group title	Crossover Phase: Brigatinib 90 mg QD/180 mg QD

Reporting group description:

Participants who experienced PD as assessed by the BIRC or received radiotherapy to the brain while on 'Crizotinib 250 mg BID' therapy in Randomized Phase were crossed over. Following 10-day washout period, crossover participants received brigatinib 90 mg, tablets, orally, QD for first 7 days followed by 180 mg, tablets, orally, QD in each 28-day cycle up to end of the study (The median duration of exposure was 17.25 months).

Reporting group title	Randomized Phase: Crizotinib 250 mg BID

Reporting group description:

Crizotinib 250 mg, tablets, BID in each 28-day cycle until disease progression, intolerable toxicity, consent withdrawal, or death (The median duration of exposure was 9.26 months).

Serious adverse events	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 136 (41.18%)	24 / 65 (36.92%)	53 / 137 (38.69%)
number of deaths (all causes)	41	22	29
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm Progression			
subjects affected / exposed	5 / 136 (3.68%)	3 / 65 (4.62%)	4 / 137 (2.92%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 2
Metastases To Meninges			

subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant Pleural Effusion			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases To Central Nervous System			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer Pain			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse Large B-Cell Lymphoma			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Breast Carcinoma			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Adenocarcinoma			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ovarian Cancer Stage I			

subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hodgkins Disease			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour Haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intracranial Tumour Haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 136 (2.94%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal Inflammation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	3 / 137 (2.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 136 (0.00%)	2 / 65 (3.08%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Performance Status Decreased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	3 / 136 (2.21%)	1 / 65 (1.54%)	6 / 137 (4.38%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary Embolism			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural Effusion			
subjects affected / exposed	3 / 136 (2.21%)	1 / 65 (1.54%)	3 / 137 (2.19%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Interstitial Lung Disease			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 136 (1.47%)	2 / 65 (3.08%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	3 / 3	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Oedema			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Distress			

subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Respiratory Failure			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory Arrest			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional State			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase			

Increased			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-Reactive Protein Increased			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Abnormal			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet Count Decreased			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral Neck Fracture			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ligament Rupture			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Herniation			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity To Various Agents			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Tamponade			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			

subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 136 (0.74%)	2 / 65 (3.08%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance Disorder			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cognitive Disorder			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory Impairment			

subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal Cord Paralysis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Central Nervous System Lesion			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Level Of Consciousness			

subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular Haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated Intravascular Coagulation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia Macrocytic			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo Positional			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 136 (1.47%)	2 / 65 (3.08%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	1 / 2	6 / 9	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 136 (1.47%)	1 / 65 (1.54%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Haemorrhage			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Colitis			

subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Obstruction			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Perforation			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis Ulcerative			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			

subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile Duct Stone			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary Retention			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular Weakness			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 136 (4.41%)	4 / 65 (6.15%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	1 / 8	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2

Urinary Tract Infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	3 / 137 (2.19%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 136 (1.47%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 136 (0.74%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	3 / 137 (2.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus Oesophagitis			

subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis Fungal			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical Pneumonia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Viral			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			

subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	0 / 136 (0.00%)	2 / 65 (3.08%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella Sepsis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Randomized Phase: Brigatinib 90 mg QD/180 QD	Crossover Phase: Brigatinib 90 mg QD/180 mg QD	Randomized Phase: Crizotinib 250 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 136 (97.06%)	63 / 65 (96.92%)	135 / 137 (98.54%)
Vascular disorders			
Hypertension			
subjects affected / exposed	44 / 136 (32.35%)	15 / 65 (23.08%)	12 / 137 (8.76%)
occurrences (all)	61	17	13
Hypotension			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	10 / 137 (7.30%)
occurrences (all)	3	0	10
Deep Vein Thrombosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	9 / 137 (6.57%)
occurrences (all)	0	0	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 136 (20.59%)	9 / 65 (13.85%)	31 / 137 (22.63%)
occurrences (all)	37	9	43
Pyrexia			
subjects affected / exposed	20 / 136 (14.71%)	9 / 65 (13.85%)	22 / 137 (16.06%)
occurrences (all)	27	11	29
Asthenia			
subjects affected / exposed	18 / 136 (13.24%)	8 / 65 (12.31%)	26 / 137 (18.98%)
occurrences (all)	24	15	30
Oedema Peripheral			
subjects affected / exposed	13 / 136 (9.56%)	6 / 65 (9.23%)	63 / 137 (45.99%)
occurrences (all)	15	6	76
Non-Cardiac Chest Pain			
subjects affected / exposed	11 / 136 (8.09%)	0 / 65 (0.00%)	10 / 137 (7.30%)
occurrences (all)	11	0	10
Malaise			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	3 / 137 (2.19%)
occurrences (all)	7	0	3
Influenza Like Illness			
subjects affected / exposed	6 / 136 (4.41%)	10 / 65 (15.38%)	11 / 137 (8.03%)
occurrences (all)	7	10	11
Peripheral Swelling			

subjects affected / exposed	5 / 136 (3.68%)	0 / 65 (0.00%)	8 / 137 (5.84%)
occurrences (all)	6	0	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	49 / 136 (36.03%)	16 / 65 (24.62%)	29 / 137 (21.17%)
occurrences (all)	78	19	37
Dyspnoea			
subjects affected / exposed	31 / 136 (22.79%)	8 / 65 (12.31%)	26 / 137 (18.98%)
occurrences (all)	36	10	33
Oropharyngeal Pain			
subjects affected / exposed	13 / 136 (9.56%)	8 / 65 (12.31%)	7 / 137 (5.11%)
occurrences (all)	17	13	8
Productive Cough			
subjects affected / exposed	12 / 136 (8.82%)	8 / 65 (12.31%)	10 / 137 (7.30%)
occurrences (all)	14	9	15
Epistaxis			
subjects affected / exposed	9 / 136 (6.62%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences (all)	11	0	0
Dysphonia			
subjects affected / exposed	8 / 136 (5.88%)	0 / 65 (0.00%)	6 / 137 (4.38%)
occurrences (all)	10	0	9
Rhinorrhoea			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	5 / 137 (3.65%)
occurrences (all)	12	0	6
Pleural Effusion			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	9 / 137 (6.57%)
occurrences (all)	2	0	9
Haemoptysis			
subjects affected / exposed	0 / 136 (0.00%)	4 / 65 (6.15%)	0 / 137 (0.00%)
occurrences (all)	0	4	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 136 (10.29%)	7 / 65 (10.77%)	12 / 137 (8.76%)
occurrences (all)	15	7	16
Depression			

subjects affected / exposed	5 / 136 (3.68%)	0 / 65 (0.00%)	8 / 137 (5.84%)
occurrences (all)	5	0	9
Anxiety			
subjects affected / exposed	0 / 136 (0.00%)	4 / 65 (6.15%)	0 / 137 (0.00%)
occurrences (all)	0	4	0
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	68 / 136 (50.00%)	31 / 65 (47.69%)	23 / 137 (16.79%)
occurrences (all)	198	59	65
Aspartate Aminotransferase Increased			
subjects affected / exposed	35 / 136 (25.74%)	17 / 65 (26.15%)	36 / 137 (26.28%)
occurrences (all)	105	31	62
Alanine Aminotransferase Increased			
subjects affected / exposed	31 / 136 (22.79%)	11 / 65 (16.92%)	49 / 137 (35.77%)
occurrences (all)	71	24	92
Lipase Increased			
subjects affected / exposed	31 / 136 (22.79%)	18 / 65 (27.69%)	23 / 137 (16.79%)
occurrences (all)	77	36	42
Amylase Increased			
subjects affected / exposed	25 / 136 (18.38%)	14 / 65 (21.54%)	13 / 137 (9.49%)
occurrences (all)	84	23	20
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	17 / 136 (12.50%)	4 / 65 (6.15%)	18 / 137 (13.14%)
occurrences (all)	35	6	23
Blood Cholesterol Increased			
subjects affected / exposed	13 / 136 (9.56%)	5 / 65 (7.69%)	1 / 137 (0.73%)
occurrences (all)	30	8	1
Blood Creatinine Increased			
subjects affected / exposed	8 / 136 (5.88%)	0 / 65 (0.00%)	20 / 137 (14.60%)
occurrences (all)	19	0	38
Electrocardiogram Qt Prolonged			
subjects affected / exposed	8 / 136 (5.88%)	5 / 65 (7.69%)	8 / 137 (5.84%)
occurrences (all)	18	8	13
Blood Lactate Dehydrogenase Increased			

subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	5 / 137 (3.65%)
occurrences (all)	11	0	5
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	5 / 136 (3.68%)	0 / 65 (0.00%)	8 / 137 (5.84%)
occurrences (all)	7	0	9
Neutrophil Count Decreased			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	14 / 137 (10.22%)
occurrences (all)	4	0	60
Blood Insulin Increased			
subjects affected / exposed	0 / 136 (0.00%)	4 / 65 (6.15%)	0 / 137 (0.00%)
occurrences (all)	0	4	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	10 / 136 (7.35%)	0 / 65 (0.00%)	22 / 137 (16.06%)
occurrences (all)	14	0	26
Sinus Bradycardia			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	11 / 137 (8.03%)
occurrences (all)	14	0	14
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 136 (22.79%)	16 / 65 (24.62%)	25 / 137 (18.25%)
occurrences (all)	52	19	37
Dizziness			
subjects affected / exposed	23 / 136 (16.91%)	12 / 65 (18.46%)	29 / 137 (21.17%)
occurrences (all)	28	15	37
Paraesthesia			
subjects affected / exposed	12 / 136 (8.82%)	5 / 65 (7.69%)	9 / 137 (6.57%)
occurrences (all)	12	7	14
Dysgeusia			
subjects affected / exposed	5 / 136 (3.68%)	0 / 65 (0.00%)	20 / 137 (14.60%)
occurrences (all)	6	0	23
Hypoaesthesia			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	9 / 137 (6.57%)
occurrences (all)	3	0	14
Taste Disorder			

subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	8 / 137 (5.84%)
occurrences (all)	3	0	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 136 (8.82%)	5 / 65 (7.69%)	8 / 137 (5.84%)
occurrences (all)	18	5	8
Eye disorders			
Vision Blurred			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	14 / 137 (10.22%)
occurrences (all)	8	0	15
Photopsia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	29 / 137 (21.17%)
occurrences (all)	1	0	32
Visual Impairment			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	23 / 137 (16.79%)
occurrences (all)	1	0	27
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	78 / 136 (57.35%)	17 / 65 (26.15%)	77 / 137 (56.20%)
occurrences (all)	213	31	206
Nausea			
subjects affected / exposed	44 / 136 (32.35%)	11 / 65 (16.92%)	81 / 137 (59.12%)
occurrences (all)	97	18	135
Vomiting			
subjects affected / exposed	30 / 136 (22.06%)	9 / 65 (13.85%)	59 / 137 (43.07%)
occurrences (all)	47	9	129
Constipation			
subjects affected / exposed	26 / 136 (19.12%)	10 / 65 (15.38%)	57 / 137 (41.61%)
occurrences (all)	33	13	77
Abdominal Pain			
subjects affected / exposed	18 / 136 (13.24%)	0 / 65 (0.00%)	20 / 137 (14.60%)
occurrences (all)	25	0	24
Dyspepsia			
subjects affected / exposed	15 / 136 (11.03%)	0 / 65 (0.00%)	23 / 137 (16.79%)
occurrences (all)	18	0	36
Stomatitis			

subjects affected / exposed	12 / 136 (8.82%)	5 / 65 (7.69%)	9 / 137 (6.57%)
occurrences (all)	33	5	9
Abdominal Pain Upper			
subjects affected / exposed	11 / 136 (8.09%)	0 / 65 (0.00%)	26 / 137 (18.98%)
occurrences (all)	15	0	37
Dry Mouth			
subjects affected / exposed	8 / 136 (5.88%)	0 / 65 (0.00%)	6 / 137 (4.38%)
occurrences (all)	8	0	10
Dysphagia			
subjects affected / exposed	2 / 136 (1.47%)	0 / 65 (0.00%)	12 / 137 (8.76%)
occurrences (all)	2	0	14
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	16 / 137 (11.68%)
occurrences (all)	1	0	23
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	28 / 136 (20.59%)	6 / 65 (9.23%)	8 / 137 (5.84%)
occurrences (all)	34	6	11
Rash			
subjects affected / exposed	25 / 136 (18.38%)	6 / 65 (9.23%)	4 / 137 (2.92%)
occurrences (all)	34	9	4
Dermatitis Acneiform			
subjects affected / exposed	13 / 136 (9.56%)	5 / 65 (7.69%)	3 / 137 (2.19%)
occurrences (all)	16	6	3
Rash Erythematous			
subjects affected / exposed	9 / 136 (6.62%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences (all)	12	0	1
Dry Skin			
subjects affected / exposed	8 / 136 (5.88%)	0 / 65 (0.00%)	6 / 137 (4.38%)
occurrences (all)	8	0	7
Rash Maculo-Papular			
subjects affected / exposed	8 / 136 (5.88%)	9 / 65 (13.85%)	5 / 137 (3.65%)
occurrences (all)	11	13	5
Eczema			
subjects affected / exposed	8 / 136 (5.88%)	6 / 65 (9.23%)	3 / 137 (2.19%)
occurrences (all)	10	6	4

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	35 / 136 (25.74%)	11 / 65 (16.92%)	22 / 137 (16.06%)
occurrences (all)	43	12	22
Arthralgia			
subjects affected / exposed	27 / 136 (19.85%)	9 / 65 (13.85%)	17 / 137 (12.41%)
occurrences (all)	33	10	19
Muscle Spasms			
subjects affected / exposed	20 / 136 (14.71%)	17 / 65 (26.15%)	15 / 137 (10.95%)
occurrences (all)	27	27	18
Musculoskeletal Pain			
subjects affected / exposed	15 / 136 (11.03%)	10 / 65 (15.38%)	11 / 137 (8.03%)
occurrences (all)	19	10	12
Myalgia			
subjects affected / exposed	14 / 136 (10.29%)	11 / 65 (16.92%)	11 / 137 (8.03%)
occurrences (all)	17	16	12
Musculoskeletal Chest Pain			
subjects affected / exposed	12 / 136 (8.82%)	0 / 65 (0.00%)	10 / 137 (7.30%)
occurrences (all)	13	0	13
Pain In Extremity			
subjects affected / exposed	9 / 136 (6.62%)	5 / 65 (7.69%)	19 / 137 (13.87%)
occurrences (all)	9	5	24
Muscular Weakness			
subjects affected / exposed	0 / 136 (0.00%)	5 / 65 (7.69%)	0 / 137 (0.00%)
occurrences (all)	0	5	0
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	18 / 136 (13.24%)	6 / 65 (9.23%)	12 / 137 (8.76%)
occurrences (all)	24	7	21
Nasopharyngitis			
subjects affected / exposed	12 / 136 (8.82%)	5 / 65 (7.69%)	15 / 137 (10.95%)
occurrences (all)	16	5	28
Urinary Tract Infection			
subjects affected / exposed	10 / 136 (7.35%)	5 / 65 (7.69%)	11 / 137 (8.03%)
occurrences (all)	14	6	11
Pneumonia			

subjects affected / exposed	10 / 136 (7.35%)	6 / 65 (9.23%)	5 / 137 (3.65%)
occurrences (all)	13	7	5
Respiratory Tract Infection			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	3 / 137 (2.19%)
occurrences (all)	8	0	3
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	16 / 136 (11.76%)	7 / 65 (10.77%)	28 / 137 (20.44%)
occurrences (all)	20	7	36
Hyperglycaemia			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	6 / 137 (4.38%)
occurrences (all)	12	0	6
Hypophosphataemia			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	5 / 137 (3.65%)
occurrences (all)	9	0	6
Hypokalaemia			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	1 / 137 (0.73%)
occurrences (all)	7	0	1
Hypercholesterolaemia			
subjects affected / exposed	7 / 136 (5.15%)	0 / 65 (0.00%)	0 / 137 (0.00%)
occurrences (all)	14	0	0
Hypocalcaemia			
subjects affected / exposed	3 / 136 (2.21%)	0 / 65 (0.00%)	11 / 137 (8.03%)
occurrences (all)	3	0	11
Hypoalbuminaemia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	11 / 137 (8.03%)
occurrences (all)	1	0	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2018	Amendment 2.0: The primary purpose of this amendment was to make following changes: The primary reason for this amendment was to remove hormonal contraception methods from permitted treatment/therapy and from the definition of highly effective contraceptive methods. The rationale for this change was based on in vitro Cytochrome P450 (CYP3A) induction observed with brigatinib, which may decrease concentrations of CYP3A substrates, including hormonal contraceptives. Coadministration of brigatinib with hormonal contraceptives can result in decreased concentrations and loss of efficacy of hormonal contraceptives. Additional protocol deviation language was added per the sponsor's updated template.
12 May 2020	Amendment 3.0: The primary purpose of this amendment was to make following changes: The primary reasons for this amendment are to update the "final statistical analysis" and "End-of Study" due to achievement of the primary efficacy endpoint at the pre-planned interim analysis. The approximate duration of patient participation is 4 years which was added. Also that the primary analysis of the primary endpoint will be performed at the End-of-Study if the study ended before 198 events progression-free survival (PFS) events were observed. The analysis of the final assessment of overall survival (OS) was added and will also be performed at the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported