Clinical trial results:
A phase III multicenter, randomized study of oral LDK378 versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer

Summary

EudraCT number	2013-000319-26
Trial protocol	SE AT IT NL DE ES GB FR GR HU IE PL DK NO PT
Global end of trial date	07 January 2024

Results information

Result version number	v1 (current)
This version publication date	29 December 2024
First version publication date	29 December 2024

Trial information

Trial identification

Sponsor protocol code	CLDK378A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01828099
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	07 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to compare the antitumor activity of ceritinib versus chemotherapy, as measured by progression free survival (PFS) determined by a Blinded Independent Review Committee (BIRC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2013
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	Austria: 11
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Thailand: 28
Country: Number of subjects enrolled	Taiwan: 34
Country: Number of subjects enrolled	India: 15
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Türkiye: 5
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Germany: 10

Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	China: 45
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Korea, Republic of: 8
Worldwide total number of subjects	376
EEA total number of subjects	157

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)	295
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in 134 centers across 27 countries.

Pre-assignment

Screening details:

Participants had to satisfy all the inclusion criteria none of the exclusion criteria prior to randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceritinib

Arm description:

Ceritinib administered continuously through oral dosing at a dosage of 750 mg once daily in fasted state

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ceritinib was supplied as 150 mg hard gelatin capsules and was administered orally, fasting, once daily at a dose of 750 mg on a continuous dosing schedule (5 x 150 mg capsules).

Arm title	Chemotherapy

Arm description:

Pemetrexed plus cisplatin or carboplatin (based on Investigator’s choice) for 4 cycles (Induction) followed by pemetrexed as single agent (Maintenance)

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin was administered by slow intravenous infusion at a dose of 75 mg/m2 every 21 days.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered as intravenous infusion (AUC 5-6) on Day 1 of every cycle

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed was administered at a dose of 500 mg/m2 as an intravenous infusion on Day 1 of each 21-day cycle

Number of subjects in period 1	Ceritinib	Chemotherapy
Started	189	187
Treated	189	175
Completed	0	0
Not completed	189	187
Adverse event, serious fatal	10	12
Physician decision	17	16
Study terminated by Sponsor	13	1
Adverse event, non-fatal	24	23
Non-compliance with study treatment	1	-
Protocol deviation	1	-
Lost to follow-up	2	1
Progressive disease	99	107
Subject/guardian decision	22	26
No longer requires treatment	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ceritinib
Reporting group description:	
Ceritinib administered continuously through oral dosing at a dosage of 750 mg once daily in fasted state	
Reporting group title	Chemotherapy
Reporting group description:	
Pemetrexed plus cisplatin or carboplatin (based on Investigator's choice) for 4 cycles (Induction) followed by pemetrexed as single agent (Maintenance)	

Reporting group values	Ceritinib	Chemotherapy	Total
Number of subjects	189	187	376
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)	143	152	295
From 65-84 years	46	35	81
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	54.5	53.3	
standard deviation	± 12.76	± 12.49	-
Sex: Female, Male			
Units:			
Female	102	114	216
Male	87	73	160
Race/Ethnicity, Customized			
Units: Subjects			
Asian	76	82	158
Black	3	3	6
Caucasian	104	98	202
Native American	3	2	5
Other	3	2	5

End points

End points reporting groups

Reporting group title	Ceritinib
Reporting group description:	
Ceritinib administered continuously through oral dosing at a dosage of 750 mg once daily in fasted state	
Reporting group title	Chemotherapy
Reporting group description:	
Pemetrexed plus cisplatin or carboplatin (based on Investigator's choice) for 4 cycles (Induction) followed by pemetrexed as single agent (Maintenance)	

Primary: Progression Free Survival (PFS) by Blinded Independent Review Committee (BIRC)

End point title	Progression Free Survival (PFS) by Blinded Independent Review Committee (BIRC)
End point description:	
PFS is defined as the time from the date of randomization to the date of the first radiologically documented disease progression (as assessed by BIRC per RECIST 1.1) or death due to any cause. A patient who had not progressed or died at the date of the analysis cut-off or had received another anticancer therapy had their PFS censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. The distribution of PFS was estimated using the Kaplan-Meier (KM) method.	
End point type	Primary
End point timeframe:	
From the date of randomization to the date of first radiologically documented disease progression or death due to any cause, up to approximately 34 months	

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Months				
median (confidence interval 95%)	16.6 (12.6 to 27.2)	8.1 (5.8 to 11.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Ceritinib v Chemotherapy
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.73

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS defined as time from date of randomization to date of death due to any cause.
If the patient was alive at the date of the analysis cut-off or lost to follow-up, then OS was censored at the last contact date prior to data cut-off date. The distribution of OS was estimated using the KM method.

End point type	Secondary

End point timeframe:

From date of randomization to date of death due to any cause, up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Months				
median (confidence interval 95%)	62.9 (44.2 to 77.6)	40.7 (28.5 to 54.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by BIRC assessment

End point title	Overall Response Rate (ORR) by BIRC assessment

End point description:

ORR is defined as the percentage of patients with a best overall response defined as complete response (CR) or or partial response (PR) measured by BIRC per RECIST 1.1. CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Percentage of participants				
number (confidence interval 95%)	72.5 (65.5 to 78.7)	26.7 (20.5 to 33.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by investigator assessment

End point title	Duration of Response (DOR) by investigator assessment

End point description:

DOR is defined as the time from date of first documented CR or PR to date of first documented disease progression (measured by investigator assessment per RECIST 1.1) or death due to any cause.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
If a patient had not had an event, DOR was censored at the date of last adequate tumor assessment.
Patients who had never achieved a best overall response of CR or PR were excluded from the analysis.
The distribution function of DOR was estimated using the KM method.

End point type	Secondary

End point timeframe:

From first documented response to first documented disease progression or death, assessed up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	62		
Units: Months				
median (confidence interval 95%)	22.6 (17.7 to 26.2)	9.8 (6.1 to 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by BIRC assessment

End point title	Duration of Response (DOR) by BIRC assessment

End point description:

DOR is defined as the time from date of first documented CR or PR to date of first documented disease progression (measured by BIRC assessment per RECIST 1.1) or death due to any cause. CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
If a patient had not had an event, DOR was censored at the date of last adequate tumor assessment.
Patients who had never achieved a best overall response of CR or PR were excluded from the analysis.
The distribution function of DOR was estimated using the KM method.

End point type	Secondary

End point timeframe:

From first documented response to first documented disease progression or death, assessed up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	50		
Units: Months				
median (confidence interval 95%)	23.9 (16.6 to 9999)	11.1 (7.8 to 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by investigator assessment

End point title	Overall Response Rate (ORR) by investigator assessment

End point description:

ORR is defined as the percentage of patients with a best overall response defined as complete response (CR) or or partial response (PR) measured by investigator assessment per RECIST 1.1.
CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Percentage of participants				
number (confidence interval 95%)	73.5 (66.7 to 79.7)	33.2 (26.5 to 40.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by investigator assessment

End point title	Disease Control Rate (DCR) by investigator assessment

End point description:

DCR is defined as the percentage of patients with best overall response of CR, PR, or stable disease (SD) measured by investigator assessment per RECIST 1.1.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Percentage of participants				
number (confidence interval 95%)	89.4 (84.1 to 93.4)	75.9 (69.2 to 81.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by BIRC assessment

End point title	Disease Control Rate (DCR) by BIRC assessment

End point description:

DCR is defined as the percentage of patients with best overall response of CR, PR, or stable disease (SD) measured by BIRC assessment per RECIST 1.1.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Percentage of participants				
number (confidence interval 95%)	84.7 (78.7 to 89.5)	73.8 (66.9 to 79.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by investigator assessment

End point title	Time to response (TTR) by investigator assessment

End point description:

TTR is defined as the time from date of randomization to date of first documented response (CR or PR) measured by investigator assessment per RECIST 1.1.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Patients who had not achieved a confirmed CR or PR were censored at the last adequate tumor assessment date when they had not had a PFS event or at maximum follow-up when they had had a PFS event

End point type	Secondary

End point timeframe:

From randomization to date of first documented response, up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	62		
Units: Weeks				
median (full range (min-max))	6.29 (5.1 to 71.9)	12.71 (4.7 to 461.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by BIRC assessment

End point title	Time to response (TTR) by BIRC assessment

End point description:

TTR is defined as the time from date of randomization to date of first documented response (CR or PR) measured by BIRC assessment per RECIST 1.1.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Patients who had not achieved a confirmed CR or PR were censored at the last adequate tumor assessment date when they had not had a PFS event or at maximum follow-up when they had had a PFS event.

End point type	Secondary

End point timeframe:

From randomization to date of first documented response, up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	50		
Units: Weeks				
median (full range (min-max))	6.14 (5.1 to 61.7)	13.36 (5.1 to 90.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by investigator assessment

End point title	PFS by investigator assessment

End point description:

PFS is defined as the time from the date of randomization to the date of the first radiologically documented disease progression (as assessed by investigator assessment per RECIST 1.1) or death due to any cause.
A patient who had not progressed or died at the date of the analysis cut-off or had received another anticancer therapy had their PFS censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. The distribution of PFS was estimated using the KM method.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of first radiologically documented disease progression or death due to any cause, up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Months				
median (confidence interval 95%)	16.8 (13.5 to 22.8)	7.2 (5.8 to 9.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial disease control rate (IDCR)

End point title	Intracranial disease control rate (IDCR)

End point description:

IDCR is defined as the DCR based on lesions in brain (target, non-target lesions and new lesions, if applicable) and calculated as the percentage of patients with a best overall response of CR or PR or SD (or non-CR/nonPD) in the brain per modified RECIST 1.1 as assessed by BIRC neuro-radiologist.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of participants				
number (confidence interval 95%)	86.4 (65.1 to 97.1)	90.9 (70.8 to 98.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall intracranial response rate (OIRR)

End point title	Overall intracranial response rate (OIRR)

End point description:

OIRR is defined as the ORR based on lesions in brain (target, non-target lesions and new lesions, if applicable) and calculated as the percentage of patients with a best overall confirmed response of CR or PR in the brain per modified RECIST 1.1 as assessed by BIRC neuroradiologist.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of participants				
number (confidence interval 95%)	72.7 (49.8 to 89.3)	27.3 (10.7 to 50.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive 10 point deterioration in the composite endpoint of pain, cough or dyspnea in the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire

End point title	Time to definitive 10 point deterioration in the composite endpoint of pain, cough or dyspnea in the European

	Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire

End point description:

The EORTC QLQ-LC13 complemented the QLQ-C30 and measured disease symptoms and treatment-related adverse effects. The lung cancer module incorporated one multi-item scale to assess dyspnea and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms.
Time to definitive symptom deterioration for the composite endpoint was defined as the time from the date of randomization to the earliest date when the patient's score showed a 10 point or higher increase from baseline in any of the symptoms (pain, cough or dyspnea) as per EORTC QLQ-LC13 (with no later change below this threshold i.e., <10 points was observed or if this increase was observed at the last assessment for the patient) or death due to any cause.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Months				
median (confidence interval 95%)	76.0 (42.2 to 9999)	14.9 (11.1 to 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of intracranial response (DOIR)

End point title	Duration of intracranial response (DOIR)

End point description:

DOIR is defined as the DOR based on lesions in brain (target, non-target lesions and new lesions, if applicable) and calculated from the time of first documented response of CR or PR to the date of the first documented disease progression in the brain or death due to any cause per modified RECIST 1.1 as assessed by BIRC neuro-radiologist.
CR: Disappearance of all lesions with lymph nodes measuring < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From first documented response to first documented disease progression in the brain or death, assessed up to approximately 34 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	6		
Units: Months				
median (confidence interval 95%)	16.6 (8.1 to 9999)	9999 (1.5 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration in the composite endpoint of pain, cough or dyspnea in the lung cancer symptom scale (LCSS)

End point title	Time to definitive deterioration in the composite endpoint of pain, cough or dyspnea in the lung cancer symptom scale (LCSS)

End point description:

The LCSS patient scale used a 24-hour recall period and contained nine items: six measuring major symptoms for lung cancer (appetite loss, fatigue, cough, dyspnea, hemoptysis, pain), and three summary items related to total symptom distress, normal activity status, and overall quality of life. The LCSS used a 100mm visual analog scale (VAS) to measure the intensity of patient responses, with zero corresponding to the lowest rating (best status) and 100 representing the highest rating (worst status). Time to definitive deterioration for the composite endpoint was defined as the time from the date of randomization to the earliest date when the patient's score showed a 10 point or higher increase from baseline in any of the LCSS scores related to pain in the chest, cough, or dyspnea (with no later change below this threshold i.e., <10 points was observed or if this increase was observed at the last assessment for the patient) or death due to any cause.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Months				
median (confidence interval 95%)	104.0 (76.0 to 9999)	36.1 (18.4 to 100.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the EORTC-QLQ C30

End point title	Least Squares Mean Scores on the EORTC-QLQ C30

End point description:

The EORTC QLQ-C30 contained 30 items and was of both multi-item scales and single-item measures,

including 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status (GHS)/quality of life (QoL) scale. Items were assessed on a 4- or 7-level Likert scale, ranging from 1="very poor" to 7= "excellent" for GHS items and 1= "not at all" to 4= "very much" for all other items. The scores of the scales were averaged from the scores of the component items, transformed, and analyzed on a 0 - 100 scale. A high score represented a higher response level. The scores were analyzed using repeated measurement model for longitudinal data, including terms for visit, treatment, treatment by time interaction, strata and baseline score. Overall mean and standard error were obtained

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	161		
Units: Score on a scale				
least squares mean (standard error)				
Global Health Status/QoL (n= 181, 161)	69.4 (± 0.71)	63.7 (± 0.98)		
Physical Functioning (n= 182, 161)	83.5 (± 0.78)	77.6 (± 1.07)		
Emotional Functioning (n= 181, 161)	82.3 (± 0.70)	76.6 (± 0.97)		
Social Functioning (n= 181, 161)	79.0 (± 1.01)	75.4 (± 1.38)		
Cognitive Functioning (n= 181, 161)	86.7 (± 0.68)	84.0 (± 0.94)		
Role Functioning (n= 182, 161)	79.5 (± 1.03)	71.3 (± 1.44)		
Fatigue (n= 182, 161)	25.9 (± 0.84)	31.4 (± 1.17)		
Nausea and Vomiting (n= 182, 161)	11.8 (± 0.58)	11.6 (± 0.82)		
Pain (n= 181, 161)	14.7 (± 0.75)	16.9 (± 1.05)		
Dyspnea (n= 182, 161)	15.0 (± 0.75)	22.1 (± 1.05)		
Insomnia (n= 182, 161)	14.8 (± 0.78)	21.1 (± 1.09)		
Appetite Loss (n= 182, 161)	15.9 (± 0.82)	19.3 (± 1.15)		
Constipation (n= 182, 161)	8.1 (± 0.60)	13.0 (± 0.84)		
Diarrhea (n= 181, 161)	25.7 (± 0.80)	4.6 (± 1.12)		
Financial Difficulties (n= 181, 161)	19.9 (± 1.19)	23.8 (± 1.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the EORTC QLQ- LC13

End point title	Least Squares Mean Scores on the EORTC QLQ- LC13

End point description:

The EORTC QLQ-LC13 was used in conjunction with the EORTC QLQ-C30 and provided information on an additional 13 items specifically related to lung cancer. The lung cancer module incorporated one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Items were scored on a 4-point Likert scale ranging from 1="not at all" to 4="very much". For the multi-item scale, the scores were averaged from the scores of the component items, transformed, and then analyzed on a 0 - 100 scale. For the single item scale, raw scores were transformed and analyzed on a 0-100 scale. A high score indicated a high level of symptoms

The scores were analyzed using repeated measurement model for longitudinal data, including terms for visit, treatment, treatment by time interaction, strata and baseline score. Overall mean and standard error were obtained.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	159		
Units: Score on a scale				
least squares mean (standard error)				
Dyspnoea (n= 181, 158)	16.2 (± 0.74)	23.3 (± 1.02)		
Pain in chest (n= 181, 159)	9.4 (± 0.59)	11.8 (± 0.82)		
Pain in Arm or Shoulder (n= 181, 157)	10.6 (± 0.69)	12.3 (± 0.97)		
Pain in Other Parts (n= 180, 157)	12.5 (± 0.71)	15.0 (± 1.01)		
Coughing (n= 181, 159)	14.7 (± 0.63)	23.0 (± 0.88)		
Sore Mouth (n= 181, 159)	3.0 (± 0.35)	6.8 (± 0.49)		
Dysphagia (n= 181, 159)	4.1 (± 0.37)	5.5 (± 0.52)		
Peripheral Neuropathy (n= 181, 159)	9.7 (± 0.69)	16.0 (± 0.96)		
Alopecia (n= 181, 159)	6.8 (± 0.70)	13.3 (± 0.95)		
Haemoptysis (n= 181, 159)	0.7 (± 0.18)	1.5 (± 0.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the Lung Cancer Symptom Scale (LCSS)

End point title	Least Squares Mean Scores on the Lung Cancer Symptom Scale (LCSS)

End point description:

The LCSS consisted of 9 individual items; 6 measured lung cancer symptoms (appetite, fatigue, cough, dyspnea, hemoptysis, and pain); the remaining 3 items measured general lung cancer symptom distress, interference with daily activities and overall QoL. Each item was scored on a 100-millimeter Visual Analogue Scale (VAS), with scores ranging from 0 to 100 (0 = best outcome).
Total score was calculated as the average of the aggregate score of all 9 items. Scores ranged from 0 to 100, with higher total scores indicating a greater overall impact of symptoms on the patient's QoL. The Symptom Burden Index (SBI) was calculated as the average of the six symptom items. It also ranged from 0 to 100, with higher scores indicating greater symptom burden.
Scores were analyzed using repeated measurement model for longitudinal data, including terms for visit, treatment, treatment by time interaction, strata and baseline score. Overall mean and standard error were obtained.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	161		
Units: Score on a Scale				
least squares mean (standard error)				
Total Score (n= 181, 160)	19.1 (± 1.18)	24.7 (± 1.31)		
Appetite Loss (n= 183, 161)	20.9 (± 1.35)	25.1 (± 1.58)		
Fatigue (n= 183, 161)	27.4 (± 1.50)	33.9 (± 1.74)		
Cough (n= 183, 161)	8.0 (± 0.87)	15.1 (± 1.02)		
Shortness of Breath (n= 183, 161)	18.8 (± 1.40)	25.5 (± 1.62)		
Hemoptysis (n= 183, 160)	0.7 (± 0.37)	1.9 (± 0.44)		
Pain (n= 183, 161)	11.6 (± 1.16)	14.9 (± 1.35)		
Total Symptom Distress (n= 182, 161)	20.5 (± 1.75)	29.3 (± 2.02)		
Normal Activity Status (n= 183, 161)	23.6 (± 1.59)	33.5 (± 1.84)		
Overall Quality of Life (n= 182, 161)	27.4 (± 1.56)	35.3 (± 1.75)		
LCSS Average Symptom Burden Index (n= 183, 160)	14.7 (± 0.91)	19.4 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the EQ-5D-5L visual analogue score (VAS)

End point title	Least Squares Mean Scores on the EQ-5D-5L visual analogue score (VAS)

End point description:

The EQ-5D-5L questionnaire is a standardized measure of health status. The EQ-5D-5L descriptive system comprises of the 5 following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Along with the five dimensions of health, the EQ-5D-5L includes a VAS where respondents rate their overall health status on a scale from 0 to 100, where 0 represents the worst possible health state and 100 represents the best possible health state. A positive change from baseline indicates improvement.
The scores were analyzed using repeated measurement model for longitudinal data, including terms for visit, treatment, treatment by time interaction, strata and baseline score. Overall mean and standard error were obtained.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	156		
Units: Score on a Scale				
least squares mean (standard error)	77.2 (± 0.65)	74.1 (± 0.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of LDK378

End point title	Cmax of LDK378[1]

End point description:

The observed maximum plasma concentration following administration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose, 1, 2, 4, 6, 8 and 24 hours post-dose. Cycle=21 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable for one arm (patients with LDK378 administration)

End point values	Ceritinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: nanogram (ng) / mililiter (ml)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	162 (± 106.9)			
Cycle 2 Day 1	794 (± 39.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the EQ-5D-5L index

End point title	Least Squares Mean Scores on the EQ-5D-5L index

End point description:

The EQ-5D-5L descriptive system provides a profile of the participant's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each of these dimensions, the participant self-assigned a score: from 1 (no problems) to 5 (extreme problems). The 5 digit health states obtained for each dimension was converted into a single mean index value based on the EQ-5D crosswalk value set for the UK using the time trade-off method. This index ranges from -0.594 (worst health) to 1.0 (best health).
The scores were analyzed using repeated measurement model for longitudinal data, including terms for visit, treatment, treatment by time interaction, strata and baseline score. Overall mean and standard error were obtained.

End point type	Secondary

End point timeframe:

Screening, treatment phase (Cycles 2, 3 then every 2nd cycle until Month 33; after Month 33, every 9 or 12 weeks, end of treatment); follow-up phase (Every 6 weeks until Month 33; after Month 33 every 9 or 12 weeks) up to approximately 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	159		
Units: Score on a Scale				
least squares mean (standard error)	0.80 (± 0.01)	0.75 (± 0.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of LDK378

End point title	Tmax of LDK378[2]

End point description:

The time to reach peak or maximum concentration (Tmax) was assessed. Actual recorded sampling times were considered for the calculations

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose, 1, 2, 4, 6, 8 and 24 hours post-dose. Cycle=21 days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable for one arm (patients with LDK378 administration)

End point values	Ceritinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1	6.00 (4.00 to 8.00)			
Cycle 2 Day 1	6.00 (6.00 to 24.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast of LDK378

End point title	Tlast of LDK378[3]

End point description:

The time to last quantifiable concentration. Actual recorded sampling times were considered for the calculations

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose, 1, 2, 4, 6, 8 and 24 hours post-dose. Cycle=21 days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable for one arm (patients with LDK378 administration)

End point values	Ceritinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1	24.0 (23.7 to 24.2)			
Cycle 2 Day 1	24.0 (23.8 to 24.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24 of LDK378

End point title	AUC0-24 of LDK378[4]

End point description:

The area under the plasma concentration-time curve calculated from time zero to 24 hours

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose, 1, 2, 4, 6, 8 and 24 hours post-dose. Cycle=21 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only applicable for one arm (patients with LDK378 administration)

End point values	Ceritinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours*ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	2540 (± 113.1)			
Cycle 2 Day 1	16600 (± 44.0)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

Pre-treatment: From randomization to start of treatment.
On-Treatment: From start of treatment to 30 days post-treatment or start of crossover treatment.
Extension treatment: From start of crossover treatment to 30 days post-crossover treatment.
Post-treatment: From 31 days after last dose of treatment (including crossover treatment) to the end of study.

End point type	Post-hoc

End point timeframe:

Pre-treatment: up to 28 days; On-Treatment: up to approx. 120 months; Extension treatment: up to approx. 108 months; Post-treatment: up to approx. 120 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	187		
Units: Participants				
Pre-treatment	0	3		
On-Treatment	15	7		
Extension-treatment	0	15		
Post-treatment	98	97		
All deaths	113	122		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to 30 days post-treatment or start of crossover treatment, up to approx. 120 months. For participants who crossed over, AEs were collected from start of crossover treatment to 30 days post-crossover treatment, up to approx. 108 months

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported, under the serious adverse events field, "number of deaths resulting from adverse events," all those deaths resulting from serious adverse events that are deemed to be causally related to treatment, by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Ceritinib

Reporting group description:

Ceritinib administered continuously through oral dosing at a dosage of 750 mg once daily in fasted state

Reporting group title	Chemotherapy to Ceritinib

Reporting group description:

patients who crossed over from chemotherapy to ceritinib treatment (administered continuously through oral dosing at a dosage of 750 mg once daily in fasted state)

Reporting group title	Chemotherapy

Reporting group description:

Pemetrexed plus cisplatin or carboplatin (based on Investigator's choice) for 4 cycles (Induction) followed by pemetrexed as single agent (Maintenance)

Serious adverse events	Ceritinib	Chemotherapy to Ceritinib	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 189 (49.21%)	47 / 100 (47.00%)	64 / 175 (36.57%)
number of deaths (all causes)	15	15	7
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Breast cancer			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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

Cancer pain			
subjects affected / exposed	0 / 189 (0.00%)	2 / 100 (2.00%)	0 / 175 (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
Metastases to meninges			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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 cancer metastatic			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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 neoplasm malignant			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Malignant neoplasm progression			
subjects affected / exposed	1 / 189 (0.53%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Metastases to central nervous system			
subjects affected / exposed	5 / 189 (2.65%)	0 / 100 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Chondrosarcoma			

subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Tumour pain			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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 artery occlusion			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Chest discomfort			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Fatigue			
subjects affected / exposed	2 / 189 (1.06%)	3 / 100 (3.00%)	3 / 175 (1.71%)
occurrences causally related to treatment / all	3 / 3	1 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 189 (1.06%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malaise			
subjects affected / exposed	2 / 189 (1.06%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 189 (1.06%)	3 / 100 (3.00%)	5 / 175 (2.86%)
occurrences causally related to treatment / all	0 / 2	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 189 (0.53%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Acute respiratory failure			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Dyspnoea			
subjects affected / exposed	6 / 189 (3.17%)	3 / 100 (3.00%)	8 / 175 (4.57%)
occurrences causally related to treatment / all	2 / 7	0 / 3	1 / 8
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Epistaxis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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

Pleuritic pain			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Interstitial lung disease			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Lung infiltration			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Painful respiration			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pleural effusion			
subjects affected / exposed	7 / 189 (3.70%)	2 / 100 (2.00%)	5 / 175 (2.86%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemoptysis			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	3 / 175 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Pneumothorax			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 189 (1.59%)	1 / 100 (1.00%)	6 / 175 (3.43%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Respiratory failure			
subjects affected / exposed	1 / 189 (0.53%)	2 / 100 (2.00%)	4 / 175 (2.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Confusional state			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Depression			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Gastrointestinal somatic symptom disorder			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 189 (1.59%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	3 / 189 (1.59%)	3 / 100 (3.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 189 (2.12%)	3 / 100 (3.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	4 / 4	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Electrocardiogram QT prolonged			

subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Liver function test abnormal			
subjects affected / exposed	0 / 189 (0.00%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Craniocerebral injury			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Craniofacial fracture			

subjects affected / exposed	1 / 189 (0.53%)	1 / 100 (1.00%)	0 / 175 (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
Fall			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Foot fracture			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Post procedural oedema			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Radiation necrosis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Road traffic accident			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Hip fracture			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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			

Acute coronary syndrome			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Myocardial infarction			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac tamponade			
subjects affected / exposed	1 / 189 (0.53%)	1 / 100 (1.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
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 arrest			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Atrial fibrillation			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Palpitations			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pericardial effusion			
subjects affected / exposed	4 / 189 (2.12%)	2 / 100 (2.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Nodal rhythm			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Brain oedema			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Dizziness			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Seizure			
subjects affected / exposed	0 / 189 (0.00%)	4 / 100 (4.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Paraparesis			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Epilepsy			

subjects affected / exposed	3 / 189 (1.59%)	0 / 100 (0.00%)	0 / 175 (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
Somnolence			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Spinal cord compression			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 189 (0.53%)	1 / 100 (1.00%)	4 / 175 (2.29%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Blindness			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
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			
Abdominal distension			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Abdominal pain			
subjects affected / exposed	0 / 189 (0.00%)	2 / 100 (2.00%)	0 / 175 (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
Abdominal pain upper			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Anal fissure			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Vomiting			
subjects affected / exposed	7 / 189 (3.70%)	2 / 100 (2.00%)	6 / 175 (3.43%)
occurrences causally related to treatment / all	6 / 7	2 / 2	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pancreatitis acute			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Oesophageal spasm			

subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Nausea			
subjects affected / exposed	6 / 189 (3.17%)	0 / 100 (0.00%)	5 / 175 (2.86%)
occurrences causally related to treatment / all	6 / 6	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Food poisoning			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Faecaloma			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Dysphagia			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	4 / 189 (2.12%)	1 / 100 (1.00%)	3 / 175 (1.71%)
occurrences causally related to treatment / all	3 / 4	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Hepatic function abnormal			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Jaundice cholestatic			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Liver injury			

subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Psoriasis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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			
Urinary retention			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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 kidney injury			
subjects affected / exposed	0 / 189 (0.00%)	5 / 100 (5.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	4 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Hydronephrosis			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Renal failure			
subjects affected / exposed	2 / 189 (1.06%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular disorder			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Back pain			
subjects affected / exposed	3 / 189 (1.59%)	3 / 100 (3.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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

Arthralgia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pathological fracture			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Infections and infestations			
Acute hepatitis B			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Appendicitis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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 abscess			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Bronchitis			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Cellulitis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Diarrhoea infectious			
subjects affected / exposed	1 / 189 (0.53%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Eye abscess			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 189 (0.53%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Helicobacter gastritis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Herpes zoster			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Influenza			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Localised infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Peritonitis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Lymphangitis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Mastoiditis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Meningitis bacterial			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Otitis media acute			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 189 (0.53%)	2 / 100 (2.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pneumonia			
subjects affected / exposed	13 / 189 (6.88%)	8 / 100 (8.00%)	9 / 175 (5.14%)
occurrences causally related to treatment / all	1 / 15	2 / 9	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 4
Pneumonia aspiration			

subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Pyomyositis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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	2 / 189 (1.06%)	0 / 100 (0.00%)	0 / 175 (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
Salmonella sepsis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Sepsis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Upper respiratory tract infection			

subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Decreased appetite			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Dehydration			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Electrolyte imbalance			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (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
Hyperglycaemia			

subjects affected / exposed	5 / 189 (2.65%)	2 / 100 (2.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	3 / 5	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 189 (1.06%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypomagnesaemia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 100 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 100 (0.00%)	0 / 175 (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
Lactic acidosis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 100 (1.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

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

Non-serious adverse events	Ceritinib	Chemotherapy to Ceritinib	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 189 (98.41%)	99 / 100 (99.00%)	166 / 175 (94.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 189 (7.94%)	8 / 100 (8.00%)	14 / 175 (8.00%)
occurrences (all)	23	11	19
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	36 / 189 (19.05%)	14 / 100 (14.00%)	38 / 175 (21.71%)
occurrences (all)	67	17	67
Face oedema			
subjects affected / exposed	3 / 189 (1.59%)	1 / 100 (1.00%)	10 / 175 (5.71%)
occurrences (all)	3	1	10
Fatigue			
subjects affected / exposed	62 / 189 (32.80%)	27 / 100 (27.00%)	53 / 175 (30.29%)
occurrences (all)	81	34	85
Influenza like illness			
subjects affected / exposed	12 / 189 (6.35%)	4 / 100 (4.00%)	4 / 175 (2.29%)
occurrences (all)	18	5	5
Non-cardiac chest pain			
subjects affected / exposed	41 / 189 (21.69%)	8 / 100 (8.00%)	18 / 175 (10.29%)
occurrences (all)	51	10	18
Oedema peripheral			
subjects affected / exposed	15 / 189 (7.94%)	11 / 100 (11.00%)	32 / 175 (18.29%)
occurrences (all)	19	13	39
Pyrexia			
subjects affected / exposed	43 / 189 (22.75%)	14 / 100 (14.00%)	22 / 175 (12.57%)
occurrences (all)	92	14	27
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	14 / 189 (7.41%)	3 / 100 (3.00%)	13 / 175 (7.43%)
occurrences (all)	19	3	17
Dyspnoea			
subjects affected / exposed	35 / 189 (18.52%)	17 / 100 (17.00%)	30 / 175 (17.14%)
occurrences (all)	43	19	33
Cough			
subjects affected / exposed	58 / 189 (30.69%)	20 / 100 (20.00%)	33 / 175 (18.86%)
occurrences (all)	94	30	47
Rhinorrhoea			
subjects affected / exposed	12 / 189 (6.35%)	3 / 100 (3.00%)	5 / 175 (2.86%)
occurrences (all)	24	3	9
Productive cough			

subjects affected / exposed	11 / 189 (5.82%)	6 / 100 (6.00%)	8 / 175 (4.57%)
occurrences (all)	12	6	9
Oropharyngeal pain			
subjects affected / exposed	16 / 189 (8.47%)	4 / 100 (4.00%)	8 / 175 (4.57%)
occurrences (all)	28	4	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 189 (11.64%)	11 / 100 (11.00%)	20 / 175 (11.43%)
occurrences (all)	26	14	30
Anxiety			
subjects affected / exposed	10 / 189 (5.29%)	2 / 100 (2.00%)	5 / 175 (2.86%)
occurrences (all)	10	2	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	121 / 189 (64.02%)	53 / 100 (53.00%)	40 / 175 (22.86%)
occurrences (all)	289	120	76
Amylase increased			
subjects affected / exposed	28 / 189 (14.81%)	16 / 100 (16.00%)	12 / 175 (6.86%)
occurrences (all)	45	36	29
Aspartate aminotransferase increased			
subjects affected / exposed	103 / 189 (54.50%)	48 / 100 (48.00%)	34 / 175 (19.43%)
occurrences (all)	245	96	54
Blood alkaline phosphatase increased			
subjects affected / exposed	58 / 189 (30.69%)	25 / 100 (25.00%)	11 / 175 (6.29%)
occurrences (all)	96	41	19
Blood bilirubin increased			
subjects affected / exposed	14 / 189 (7.41%)	1 / 100 (1.00%)	1 / 175 (0.57%)
occurrences (all)	43	3	2
Blood creatinine increased			
subjects affected / exposed	53 / 189 (28.04%)	43 / 100 (43.00%)	20 / 175 (11.43%)
occurrences (all)	107	93	28
Creatinine renal clearance decreased			
subjects affected / exposed	14 / 189 (7.41%)	10 / 100 (10.00%)	6 / 175 (3.43%)
occurrences (all)	25	28	11
Electrocardiogram QT prolonged			

subjects affected / exposed	27 / 189 (14.29%)	7 / 100 (7.00%)	2 / 175 (1.14%)
occurrences (all)	58	16	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	70 / 189 (37.04%)	30 / 100 (30.00%)	19 / 175 (10.86%)
occurrences (all)	124	41	23
Haemoglobin decreased			
subjects affected / exposed	7 / 189 (3.70%)	5 / 100 (5.00%)	13 / 175 (7.43%)
occurrences (all)	9	5	20
Lipase increased			
subjects affected / exposed	17 / 189 (8.99%)	5 / 100 (5.00%)	2 / 175 (1.14%)
occurrences (all)	68	15	2
Neutrophil count decreased			
subjects affected / exposed	6 / 189 (3.17%)	3 / 100 (3.00%)	30 / 175 (17.14%)
occurrences (all)	12	11	100
Platelet count decreased			
subjects affected / exposed	6 / 189 (3.17%)	0 / 100 (0.00%)	11 / 175 (6.29%)
occurrences (all)	33	0	17
Weight decreased			
subjects affected / exposed	51 / 189 (26.98%)	19 / 100 (19.00%)	26 / 175 (14.86%)
occurrences (all)	62	20	27
White blood cell count decreased			
subjects affected / exposed	11 / 189 (5.82%)	3 / 100 (3.00%)	34 / 175 (19.43%)
occurrences (all)	34	8	116
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	13 / 189 (6.88%)	2 / 100 (2.00%)	11 / 175 (6.29%)
occurrences (all)	15	2	14
Headache			
subjects affected / exposed	46 / 189 (24.34%)	17 / 100 (17.00%)	23 / 175 (13.14%)
occurrences (all)	118	20	29
Dysgeusia			
subjects affected / exposed	16 / 189 (8.47%)	4 / 100 (4.00%)	11 / 175 (6.29%)
occurrences (all)	16	4	13
Dizziness			

subjects affected / exposed	35 / 189 (18.52%)	8 / 100 (8.00%)	17 / 175 (9.71%)
occurrences (all)	53	12	29
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 189 (2.12%)	4 / 100 (4.00%)	17 / 175 (9.71%)
occurrences (all)	4	14	32
Neutropenia			
subjects affected / exposed	13 / 189 (6.88%)	10 / 100 (10.00%)	42 / 175 (24.00%)
occurrences (all)	34	43	107
Leukopenia			
subjects affected / exposed	7 / 189 (3.70%)	6 / 100 (6.00%)	17 / 175 (9.71%)
occurrences (all)	8	28	72
Anaemia			
subjects affected / exposed	34 / 189 (17.99%)	21 / 100 (21.00%)	63 / 175 (36.00%)
occurrences (all)	56	37	102
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 189 (2.12%)	4 / 100 (4.00%)	16 / 175 (9.14%)
occurrences (all)	4	4	16
Eye disorders			
Lacrimation increased			
subjects affected / exposed	2 / 189 (1.06%)	1 / 100 (1.00%)	10 / 175 (5.71%)
occurrences (all)	2	1	10
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	50 / 189 (26.46%)	17 / 100 (17.00%)	14 / 175 (8.00%)
occurrences (all)	70	23	23
Abdominal distension			
subjects affected / exposed	17 / 189 (8.99%)	3 / 100 (3.00%)	4 / 175 (2.29%)
occurrences (all)	24	4	6
Vomiting			
subjects affected / exposed	127 / 189 (67.20%)	54 / 100 (54.00%)	59 / 175 (33.71%)
occurrences (all)	362	122	139
Stomatitis			
subjects affected / exposed	16 / 189 (8.47%)	6 / 100 (6.00%)	19 / 175 (10.86%)
occurrences (all)	21	6	24
Nausea			

subjects affected / exposed	130 / 189 (68.78%)	49 / 100 (49.00%)	99 / 175 (56.57%)
occurrences (all)	251	78	248
Haemorrhoids			
subjects affected / exposed	7 / 189 (3.70%)	0 / 100 (0.00%)	9 / 175 (5.14%)
occurrences (all)	9	0	11
Dyspepsia			
subjects affected / exposed	18 / 189 (9.52%)	7 / 100 (7.00%)	11 / 175 (6.29%)
occurrences (all)	26	7	12
Constipation			
subjects affected / exposed	39 / 189 (20.63%)	17 / 100 (17.00%)	39 / 175 (22.29%)
occurrences (all)	57	19	53
Abdominal pain upper			
subjects affected / exposed	49 / 189 (25.93%)	12 / 100 (12.00%)	11 / 175 (6.29%)
occurrences (all)	82	17	17
Diarrhoea			
subjects affected / exposed	160 / 189 (84.66%)	76 / 100 (76.00%)	17 / 175 (9.71%)
occurrences (all)	515	172	40
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	36 / 189 (19.05%)	19 / 100 (19.00%)	15 / 175 (8.57%)
occurrences (all)	73	28	38
Dry skin			
subjects affected / exposed	10 / 189 (5.29%)	6 / 100 (6.00%)	7 / 175 (4.00%)
occurrences (all)	15	6	7
Alopecia			
subjects affected / exposed	13 / 189 (6.88%)	2 / 100 (2.00%)	16 / 175 (9.14%)
occurrences (all)	14	2	16
Pruritus			
subjects affected / exposed	25 / 189 (13.23%)	7 / 100 (7.00%)	10 / 175 (5.71%)
occurrences (all)	33	11	10
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	37 / 189 (19.58%)	6 / 100 (6.00%)	15 / 175 (8.57%)
occurrences (all)	52	8	25
Neck pain			

subjects affected / exposed	16 / 189 (8.47%)	3 / 100 (3.00%)	3 / 175 (1.71%)
occurrences (all)	19	7	3
Myalgia			
subjects affected / exposed	14 / 189 (7.41%)	2 / 100 (2.00%)	9 / 175 (5.14%)
occurrences (all)	19	2	19
Musculoskeletal chest pain			
subjects affected / exposed	15 / 189 (7.94%)	4 / 100 (4.00%)	5 / 175 (2.86%)
occurrences (all)	18	4	5
Muscular weakness			
subjects affected / exposed	11 / 189 (5.82%)	6 / 100 (6.00%)	1 / 175 (0.57%)
occurrences (all)	13	7	1
Muscle spasms			
subjects affected / exposed	12 / 189 (6.35%)	1 / 100 (1.00%)	2 / 175 (1.14%)
occurrences (all)	23	1	2
Bone pain			
subjects affected / exposed	6 / 189 (3.17%)	6 / 100 (6.00%)	4 / 175 (2.29%)
occurrences (all)	6	6	4
Back pain			
subjects affected / exposed	47 / 189 (24.87%)	14 / 100 (14.00%)	30 / 175 (17.14%)
occurrences (all)	68	16	34
Arthralgia			
subjects affected / exposed	46 / 189 (24.34%)	14 / 100 (14.00%)	28 / 175 (16.00%)
occurrences (all)	78	20	31
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 189 (5.82%)	2 / 100 (2.00%)	4 / 175 (2.29%)
occurrences (all)	19	2	5
Influenza			
subjects affected / exposed	18 / 189 (9.52%)	4 / 100 (4.00%)	8 / 175 (4.57%)
occurrences (all)	32	6	9
Nasopharyngitis			
subjects affected / exposed	22 / 189 (11.64%)	7 / 100 (7.00%)	12 / 175 (6.86%)
occurrences (all)	29	10	24
Pneumonia			
subjects affected / exposed	15 / 189 (7.94%)	7 / 100 (7.00%)	6 / 175 (3.43%)
occurrences (all)	17	12	6

Upper respiratory tract infection			
subjects affected / exposed	28 / 189 (14.81%)	9 / 100 (9.00%)	21 / 175 (12.00%)
occurrences (all)	41	20	35
Urinary tract infection			
subjects affected / exposed	11 / 189 (5.82%)	6 / 100 (6.00%)	8 / 175 (4.57%)
occurrences (all)	18	8	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	67 / 189 (35.45%)	21 / 100 (21.00%)	59 / 175 (33.71%)
occurrences (all)	99	24	92
Hyperglycaemia			
subjects affected / exposed	24 / 189 (12.70%)	12 / 100 (12.00%)	14 / 175 (8.00%)
occurrences (all)	30	21	43
Hypoalbuminaemia			
subjects affected / exposed	6 / 189 (3.17%)	7 / 100 (7.00%)	4 / 175 (2.29%)
occurrences (all)	6	9	5
Hypokalaemia			
subjects affected / exposed	17 / 189 (8.99%)	10 / 100 (10.00%)	8 / 175 (4.57%)
occurrences (all)	26	11	12
Hyponatraemia			
subjects affected / exposed	13 / 189 (6.88%)	6 / 100 (6.00%)	11 / 175 (6.29%)
occurrences (all)	14	8	12
Hypophosphataemia			
subjects affected / exposed	11 / 189 (5.82%)	3 / 100 (3.00%)	0 / 175 (0.00%)
occurrences (all)	15	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2013	At the time of release of this amendment six patients were screened for enrollment and no patient had been treated. The amendment reflected the availability of new safety data, amended the eligible study population, and clarified sections of the protocol where additional guidance was required: Limited the study population to stage IIIB patients who were not candidates for definitive multimodality therapy or stage IV, non-squamous NSCLC harboring a confirmed ALK rearrangement. Included only patients with potassium, magnesium, phosphorus and calcium (corrected for serum albumin) within normal limits. Added inclusion criteria of willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures. Added exclusion criteria to specify that for female patients treated with chemotherapy, highly effective contraception was to be used during the study and for at least 6 months after stopping treatment or as per the local label. Added exclusion criteria to specify that for male patients randomized to the chemotherapy arm they should not father a child for at least 6 months after the last dose of treatment or as per the local label. Added exclusion criteria of history of known interstitial fibrosis or interstitial lung disease, including radiation pneumonitis. Provided guidance on pneumonitis and dose modifications for patients who present with pneumonitis during study treatment.
29 May 2015	At the time of release of this amendment, 420 patients were screened for enrollment and 376 had been randomized. The amendment reflected the availability of updated safety information and clarified sections of the protocol where additional guidance was required: . Added guidance for dose modification of ceritinib for bradycardia, neutropenia, elevated liver function tests, pneumonitis, hyperglycemia, and QT prolongation . Added additional dose modification and follow up monitoring language for patients who experienced pancreatitis . Allowed radiotherapy and surgical resection as local palliative therapy of metastases for patients who developed progressive disease but were still deriving clinical benefit from ceritinib therapy as determined by the Investigator.

11 December 2015	the treatment phase. Of the 376 patients who entered the treatment phase, 75 patients entered the survival follow up phase, 16 entered the post-treatment follow up phase, and 62 entered the extension treatment phase. This amendment provided follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize the patient safety, and clarified sections of the protocol where additional guidance was required: . Dose guidance modification for QTc to provide clarification on monitoring procedure. . The secondary objectives and related endpoints were updated to include assessment of the anti-tumor activity of ceritinib versus chemotherapy in the brain, as measured by OIRR, IDCR and DOIR, as assessed by BIRC neuro-radiologist per modified RECIST 1.1 to allow selecting up to five measurable brain lesions as target lesions. . Updated End of Study definition. . Updated to clarify that patients in the chemotherapy arm in the treatment phase and patients in the post-treatment follow-up phase were allowed to cross-over to receive ceritinib therapy after BIRC-confirmed PD.
20 December 2017	At the time of release of this amendment, 376 patients have been randomized, 78 patients were in the study treatment phase and 92 patients entered the extension treatment phase. The following changes were implemented in this amendment: . BIRC was discontinued as the primary objective of the trial was achieved during primary analysis. . Treatment decisions and patient management will be based on local investigator assessment (i.e. continuation or discontinuation of study treatment in case of disease progression) . Tumor assessment frequency was updated to every 12 weeks. . PRO questionnaires frequency was updated to every 12 weeks in alignment with the schedule/visit for tumor assessments. . Tumor assessments and PROs were not continue if a new anti-cancer therapy was started in the Post Treatment Follow-Up Phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 9999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: