Clinical trial results:
A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib

Summary

EudraCT number	2012-005637-36
Trial protocol	DE IT ES FR NL GB IE BE PT
Global end of trial date	10 November 2023

Results information

Result version number	v2 (current)
This version publication date	28 March 2025
First version publication date	21 November 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLDK378A2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01828112
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	10 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the antitumor activity of LDK378 versus reference chemotherapy, as measured by progression-free survival (PFS) determined by blinded independent review committee (BIRC) per response evaluation criteria in solid tumors (RECIST) 1.1. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

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	28 June 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	Belgium: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Lebanon: 2
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Switzerland: 7

Country: Number of subjects enrolled	Türkiye: 9
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	231
EEA total number of subjects	111

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)	178
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment in countries (with number of sites): Belgium (4), Canada (1), France (9), Germany (8), Hong Kong (3), Ireland (2), Israel (2), Italy (10), Japan (12), Republic of Korea (5), Lebanon (1), Netherlands (2), Portugal (1), Russia (3), Singapore (2), Spain (11), Switzerland (2), Turkey (3), United Kingdom (5), United States (13).

Pre-assignment

Screening details:

In the treatment phase, patients were randomized 1:1 to one of the treatment arms (ceritinib or chemotherapy). In the extension treatment phase, only patients randomized to the chemotherapy arm were allowed to crossover to receive ceritinib therapy after BIRC-confirmed, RECIST-defined disease progression.

Period 1

Period 1 title	Treatment Phase (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 750 mg

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	
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:

Chemotherapy as determined by BIRC

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel, a reconstituted solution, was intravenously administered over 1 hour, at 75 mg/m^2 every 21 days.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed, a reconstituted solution, was intravenously administered over 10 minutes at 500 mg/m^2 every 21 days.

Number of subjects in period 1	Ceritinib	Chemotherapy
Started	115	116
Safety Set	115	113
Completed	0	0
Not completed	115	116
Adverse event, serious fatal	9	5
Physician decision	6	7
Adverse event, non-fatal	7	8
No longer required treatment	-	1
Pregnancy	1	-
Study terminated by sponsor	1	-
Progressive disease	79	87
Subject/guardian decision	12	8

Baseline characteristics

Reporting groups	
Reporting group title	Ceritinib
Reporting group description: Ceritinib 750 mg	
Reporting group title	Chemotherapy
Reporting group description: Chemotherapy as determined by BIRC	

Reporting group values	Ceritinib	Chemotherapy	Total
Number of subjects	115	116	231
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)	89	89	178
From 65-84 years	26	27	53
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.1	54.4	
standard deviation	± 11.96	± 11.61	-
Sex: Female, Male Units:			
Female	68	61	129
Male	47	55	102
Race/Ethnicity, Customized Units: Subjects			
Asian	30	38	68
Black	0	1	1
Caucasian	81	68	149
Other	2	4	6
Unknown	2	5	7

End points

End points reporting groups

Reporting group title	Ceritinib
Reporting group description:	
Ceritinib 750 mg	
Reporting group title	Chemotherapy
Reporting group description:	
Chemotherapy as determined by BIRC	
Subject analysis set title	Chemotherapy/Ceritinib
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients randomized to chemotherapy who crossed over to ceritinib at the extension treatment phase	

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

End point title	Progression Free Survival (PFS) per Blinded Independent Review Committee (BIRC)
End point description:	
PFS was defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause.	
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 24 months	

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: months				
median (confidence interval 95%)	5.4 (4.1 to 6.9)	1.6 (1.4 to 2.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Ceritinib v Chemotherapy
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.67

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as time from date of randomization to date of death due to any cause.

End point type	Secondary

End point timeframe:

Up to approximately 114 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: months				
median (confidence interval 95%)	17.7 (14.2 to 23.7)	20.1 (11.9 to 31.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per BIRC

End point title	Overall Response Rate (ORR) per BIRC

End point description:

ORR was defined as the percentage of participants with a best overall response defined as complete response (CR) or partial response (PR): (CR+PR) per Response Evaluation Criteria in Solid Tumors (RECIST), v. 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 54 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percentage of participants				
number (confidence interval 95%)	40.9 (31.8 to 50.4)	6.9 (3.0 to 13.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Investigator Assessment

End point title	Progression Free Survival (PFS) per Investigator Assessment

End point description:

PFS was defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause.

End point type	Secondary

End point timeframe:

Up to approximately 84 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: months				
median (confidence interval 95%)	6.2 (4.4 to 7.9)	1.6 (1.4 to 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per Investigator Assessment

End point title	Overall Response Rate (ORR) per Investigator Assessment

End point description:

ORR was defined as the percentage of participants with a best overall response defined as complete response (CR) or partial response (PR): (CR+PR) per Response Evaluation Criteria in Solid Tumors (RECIST), v. 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.

End point type	Secondary

End point timeframe:

Up to approximately 93 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percentage of participants				
number (confidence interval 95%)	44.3 (35.1 to 53.9)	6.9 (3.0 to 13.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per Investigator Assessment

End point title	Duration of Response (DOR) per Investigator Assessment

End point description:

DOR defined as the time from the first documented response (CR or PR) to the first documented progression or death due to underlying cancer. 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 93 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	8		
Units: months				
median (confidence interval 95%)	6.7 (5.5 to 8.3)	8.3 (2.8 to 69.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per BIRC

End point title	Duration of Response (DOR) per BIRC

End point description:

DOR defined as the time from the first documented response (CR or PR) to the first documented progression or death due to underlying cancer. 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 54 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	8		
Units: months				
median (confidence interval 95%)	7.6 (5.4 to 8.3)	10.4 (3.5 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) per Investigator Assessment

End point title	Time to response (TTR) per Investigator Assessment

End point description:

TTR was defined as the time from date of randomization to date of first documented response (CR or PR). 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 45 weeks

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	8		
Units: weeks				
median (full range (min-max))	6.43 (4.9 to 45.4)	14.71 (6.3 to 36.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) per BIRC

End point title	Time to Response (TTR) per BIRC

End point description:

TTR was defined as the time from date of randomization to date of first documented response (CR or PR). 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 52 weeks

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	8		
Units: weeks				
median (full range (min-max))	6.71 (4.9 to 52.3)	9.64 (5.4 to 43.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Investigator Assessment

End point title	Disease Control Rate (DCR) per Investigator Assessment

End point description:

DCR was defined as the percentage of participants with best overall response of CR, PR, or stable disease (SD). 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 93 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percentage of participants				
number (confidence interval 95%)	80.0 (71.5 to 86.9)	39.7 (30.7 to 49.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per BIRC

End point title	Disease Control Rate (DCR) per BIRC

End point description:

DCR was defined as the percentage of participants with best overall response of CR, PR, or stable disease (SD). 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 54 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percentage of participants				
number (confidence interval 95%)	76.5 (67.7 to 83.9)	37.9 (29.1 to 47.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Intracranial Response Rate (OIRR) per BIRC

End point title	Overall Intracranial Response Rate (OIRR) per BIRC

End point description:

OIRR was defined as the ORR based on lesions in brain (target, nontarget 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 18 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: percentage of participants				
number (confidence interval 95%)	10.6 (4.4 to 20.6)	3.0 (0.4 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Disease Control Rate (IDCR) per BIRC

End point title	Intracranial Disease Control Rate (IDCR) per BIRC

End point description:

IDCR was defined as the DCR based on lesions in brain (target, non-target lesions (and new lesions, if applicable) and calculated as the proportion 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 18 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: percentage of participants				
number (confidence interval 95%)	71.2 (58.7 to 81.7)	53.7 (41.1 to 66.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intracranial Response (DOIR) per BIRC

End point title	Duration of Intracranial Response (DOIR) per BIRC

End point description:

DOIR was 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:

Up to approximately 18 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	1		
Units: months				
median (confidence interval 95%)	8.3 (2.7 to 999)	16.7 (0.999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire (EORTC-QLQC30)

End point title	Least Squares Mean Scores on the European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire (EORTC-QLQC30)

End point description:

The EORTC QLQ-C30 questionnaire contained 30 items and was composed of both multi-item scales and single item measures. These included five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact), and a global health status/quality of life (QoL) scale.
All of the scales and single items ranged from 0 to 100. A high scale score represented a higher response level. Thus, a high score for a functional scale indicated a high/healthy level of functioning, a high score for the QoL indicated high QoL, but a high score for a symptom scale/single item indicated a high level of symptomatology/problems. Data from all collected time points were combined and presented using a repeated measures model for longitudinal data.

End point type	Secondary

End point timeframe:

Screening and treatment phase up to 92 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	86		
Units: score on a scale				
least squares mean (standard error)				
Global Health Status/QoL n=106,85	62.9 (± 1.13)	63.2 (± 1.74)		
Physical Functioning n=107,86	80.5 (± 1.04)	75.4 (± 1.52)		
Emotional Functioning n=106,86	82.4 (± 1.01)	80.7 (± 1.54)		
Social Functioning n=106,86	76.7 (± 1.56)	71.6 (± 2.31)		
Cognitive Functioning n=106,86	86.7 (± 0.91)	84.5 (± 1.40)		
Role Functioning n=107,86	72.6 (± 1.30)	68.7 (± 1.98)		
Fatigue n=107,86	31.1 (± 1.10)	36.1 (± 1.69)		
Nausea and Vomiting n=107,86	17.2 (± 1.08)	9.4 (± 1.69)		
Pain n=107,86	21.4 (± 1.22)	24.2 (± 1.85)		
Dyspnea n=107,86	17.4 (± 1.03)	24.0 (± 1.62)		
Insomnia n=107,86	18.9 (± 1.33)	25.6 (± 2.05)		
Appetite Loss n=107,86	21.2 (± 1.33)	13.9 (± 2.07)		
Constipation n=107,86	15.0 (± 1.31)	15.0 (± 2.00)		
Diarrhea n=106,86	29.3 (± 1.29)	11.4 (± 2.02)		
Financial Difficulties n=104,85	15.5 (± 1.41)	19.7 (± 2.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQ-LC13 Time to Definitive Deterioration

End point title	EORTC QLQ-LC13 Time to Definitive Deterioration

End point description:

The Lung Cancer module of the EORTC's quality of life questionnaire (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. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms. QLQ-LC13 time to definitive deterioration was defined as the time from randomization to the earliest date a patient shows a 10 point or higher increase from baseline in any of the ALCLC13 scores related to pain in chest, cough, or dyspnea (with no later change below this threshold), or death due to any cause. Each cycle was 21 days.

End point type	Secondary

End point timeframe:

Screening and treatment phase up to 92 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: months				
median (confidence interval 95%)	13.4 (8.4 to 16.7)	2.8 (1.0 to 5.6)		

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 patient scale uses a 24-hour recall period and contains 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 total scale used is a 100 mm visual analog scale to measure the intensity of patient responses, with zero corresponding to the lowest rating (best status) and 100 representing the highest rating (worst status). The total score was calculated as the mean of the 9 items. Data from all collected time points were combined and presented using a repeated measures model for longitudinal data. Data from all collected time points were combined and presented using a repeated measures model for longitudinal data.

End point type	Secondary

End point timeframe:

Screening and treatment phase up to 92 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	85		
Units: millimeters				
least squares mean (standard error)				
LCSS Total Score n=106,82	22.0 (± 0.87)	26.3 (± 1.33)		
Appetite Loss n=107,85	28.0 (± 1.26)	26.6 (± 1.99)		
Fatigue n=107,84	34.6 (± 1.33)	39.2 (± 2.06)		
Cough n=107,84	11.5 (± 1.01)	18.4 (± 1.56)		
Shortness of Breath n=107,85	18.2 (± 0.99)	24.8 (± 1.56)		
Hemoptysis n=107,85	1.8 (± 0.34)	2.2 (± 0.55)		
Pain n=107,85	18.2 (± 1.25)	24.3 (± 1.92)		
Total Symptom Distress n=107,85	20.7 (± 1.26)	24.6 (± 1.92)		
Normal Activity Status n=107,85	31.3 (± 1.47)	36.8 (± 2.21)		
Overall Quality of Life n=106,84	33.1 (± 1.27)	36.4 (± 1.94)		
LCSS Average Symptom Burden Index n=107,83	18.8 (± 0.77)	22.9 (± 1.20)		

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 descriptive classification consists of five dimensions of health: mobility, self-care, usual activities, anxiety/depression and pain/discomfort. Patients are requested to select the statement which best describes their condition on that day for each dimension. EQ-5D-5L index scores can range from −0.59 to 1, where 1 is the best possible health state. Each cycle was 21 days. Data from all collected time points were combined and presented using a repeated measures model for longitudinal data.

End point type	Secondary

End point timeframe:

Screening and treatment phase up to 92 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	88		
Units: score on a scale				
least squares mean (standard error)	0.7837 (± 0.01039)	0.7108 (± 0.01533)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Scores on the EQ-5D Visual Analogue Scale (VAS)

End point title	Least Squares Mean Scores on the EQ-5D Visual Analogue Scale (VAS)

End point description:

The EQ-5D descriptive classification consists of five dimensions of health: mobility, self-care, usual activities, anxiety/depression and pain/discomfort. Patients are requested to select the statement which best describes their condition on that day for each dimension. EQ VAS scores can range from 0 to 100, where 100 is the best possible health state. Data from all collected time points were combined and presented using a repeated measures model for longitudinal data.

End point type	Secondary

End point timeframe:

Screening and treatment phase up to 92 months

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	86		
Units: score on a scale				
least squares mean (standard error)	71.8 (± 0.98)	69.0 (± 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax for Ceritinib

End point title	Tmax for Ceritinib

End point description:

The time to reach peak or maximum concentration

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 and Cycle 2, Day 1: pre-dose and 1, 2, 4, 6, and 8 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	0[1]		
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 n=4,0	6.03 (4.17 to 23.6)	(to)		
Cycle 2, Day 1 n=2,0	7.15 (6.17 to 8.13)	(to)		

Notes:

[1] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax for Ceritinib

End point title	Cmax for Ceritinib

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: pre-dose and 1, 2, 4, 6, and 8 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	0[2]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=4,0	90.4 (± 49.8)	()		
Cycle 2, Day 1 n=2,0	1170 (± 17.7)	()		

Notes:

[2] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24h for Ceritinib

End point title	AUC0-24h for Ceritinib

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: pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	0[3]		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=4,0	1470 (± 65.1)	()		
Cycle 2, Day 1 n=2,0	25000 (± 19.0)	()		

Notes:

[3] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast for Ceritinib

End point title	Tlast for Ceritinib

End point description:

The time to last quantifiable concentration

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 and Cycle 2, Day 1: pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	0[4]		
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 n=4,0	24 (23.6 to 24.1)	(to)		
Cycle 2, Day 1 n=2,0	23.9 (23.7 to 24.2)	(to)		

Notes:

[4] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Accumulation Ratio (Racc) for Ceritinib

End point title	Mean Accumulation Ratio (Racc) for Ceritinib

End point description:

Accumulation ratio calculated using AUC0-24 values obtained from a dosing interval at steady-state (Cycle 2, Day 1) divided by AUC0-24 on Cycle 1, Day 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 and Cycle 2, Day 1: pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[5]		
Units: ratio				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=0,0	999 (± 999)	()		
Cycle 2, Day 1 n=1,0	15.5 (± 999)	()		

Notes:

[5] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Hoc: All Collected Deaths

End point title	Post-Hoc: All Collected Deaths

End point description:

Pre-treatment deaths: from day of patient's informed consent to the day before first dose of study treatment. On-treatment deaths: from first dose of study treatment to 30 days following the last dose of study treatment at the end of treatment phase. For crossover patients, from first dose of ceritinib at the extension treatment phase to 30 days following the last dose. Survival Follow-up deaths: from Day 31 after last dose of study treatment to the data cut-off date.

End point type	Secondary

End point timeframe:

Pre-treatment and on-treatment deaths: Up to approximately 8 years. Post-treatment survival follow-up deaths: Up to an additional 2.5 years.

End point values	Ceritinib	Chemotherapy	Chemotherapy/ Ceritinib	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	115	116	78	
Units: Participants				
Pre-treatment deaths	0	2	0	
On-treatment deaths	16	5	19	
Survival follow-up deaths	86	18	44	
All deaths	102	25	63	

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance Rate at Steady State (CLss/F) for Ceritinib

End point title	Clearance Rate at Steady State (CLss/F) for Ceritinib

End point description:

The apparent total body clearance from plasma. CLss/F is calculated from AUC0-24 assuming steady state (CLss/F=Dose/AUC0-24).

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 and Cycle 2, Day 1: pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose. Each cycle was 21 days.

End point values	Ceritinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	0[6]		
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=0,0	999 (± 999)	()		
Cycle 2, Day 1 n=2,0	30 (± 19.0)	()		

Notes:

[6] - Data for this endpoint are reported for patients with available data.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from day of first dose of study medication to last dose of study medication plus 30 days, up to approximately 8 years.

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 750 mg

Reporting group title	Chemotherapy/Ceritinib

Reporting group description:

Patients randomized to chemotherapy who crossed over to ceritinib at the extension treatment phase

Reporting group title	Chemotherapy

Reporting group description:

Chemotherapy as determined by BIRC

Serious adverse events	Ceritinib	Chemotherapy/Ceritinib	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 115 (49.57%)	45 / 78 (57.69%)	35 / 113 (30.97%)
number of deaths (all causes)	16	19	5
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Metastases to meninges			
subjects affected / exposed	0 / 115 (0.00%)	2 / 78 (2.56%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to central nervous system			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Asthenia			
subjects affected / exposed	2 / 115 (1.74%)	2 / 78 (2.56%)	3 / 113 (2.65%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Condition aggravated			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	7 / 115 (6.09%)	1 / 78 (1.28%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	2 / 7	0 / 2	1 / 2
deaths causally related to treatment / all	1 / 5	0 / 1	0 / 0

Fatigue			
subjects affected / exposed	2 / 115 (1.74%)	1 / 78 (1.28%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 115 (1.74%)	3 / 78 (3.85%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	4 / 115 (3.48%)	1 / 78 (1.28%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Pulmonary embolism			
subjects affected / exposed	0 / 115 (0.00%)	2 / 78 (2.56%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 failure			
subjects affected / exposed	3 / 115 (2.61%)	2 / 78 (2.56%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Pleural effusion			
subjects affected / exposed	5 / 115 (4.35%)	5 / 78 (6.41%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	1 / 5	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Interstitial lung disease			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Dyspnoea			
subjects affected / exposed	8 / 115 (6.96%)	4 / 78 (5.13%)	5 / 113 (4.42%)
occurrences causally related to treatment / all	1 / 8	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 1
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Anxiety			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Product issues			
Device failure			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
C-reactive protein increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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

Tracheal obstruction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 115 (1.74%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 arrest			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 / 115 (3.48%)	1 / 78 (1.28%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Pericarditis			

subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coordination abnormal			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Cognitive disorder			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Cerebellar infarction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Brain oedema			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Aphasia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Loss of consciousness			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Intracranial mass			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Headache			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	2 / 115 (1.74%)	0 / 78 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
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	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Seizure			
subjects affected / exposed	1 / 115 (0.87%)	2 / 78 (2.56%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Petit mal epilepsy			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Paraparesis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Syncope			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Febrile neutropenia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Lenticular opacities			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Visual field defect			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 disorders			
Abdominal pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 115 (1.74%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Gastric perforation			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Vomiting			
subjects affected / exposed	6 / 115 (5.22%)	5 / 78 (6.41%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	3 / 6	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nausea			

subjects affected / exposed	8 / 115 (6.96%)	4 / 78 (5.13%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	6 / 9	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematemesis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
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 toxicity			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 obstruction			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Gastritis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Hepatic lesion			

subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Hepatic failure			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Urinary bladder rupture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 failure			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 115 (1.74%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mobility decreased			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Back pain			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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			
Bronchitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Biliary tract infection			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Bacterial pyelonephritis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			

subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Pseudomembranous colitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Respiratory tract infection			
subjects affected / exposed	3 / 115 (2.61%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 115 (5.22%)	6 / 78 (7.69%)	4 / 113 (3.54%)
occurrences causally related to treatment / all	1 / 8	1 / 8	3 / 4
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Oral herpes			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Typhoid fever			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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
Nasopharyngitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Mucosal infection			

subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	0 / 113 (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 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (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
Localised infection			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Infection			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Urosepsis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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	2 / 115 (1.74%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 115 (0.87%)	1 / 78 (1.28%)	0 / 113 (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
Hyperglycaemia			
subjects affected / exposed	1 / 115 (0.87%)	3 / 78 (3.85%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 78 (1.28%)	0 / 113 (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
Decreased appetite			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ceritinib	Chemotherapy/Ceritinib	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 115 (99.13%)	76 / 78 (97.44%)	111 / 113 (98.23%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 115 (3.48%)	5 / 78 (6.41%)	4 / 113 (3.54%)
occurrences (all)	4	5	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 115 (25.22%)	13 / 78 (16.67%)	19 / 113 (16.81%)
occurrences (all)	46	18	32
Fatigue			
subjects affected / exposed	34 / 115 (29.57%)	17 / 78 (21.79%)	32 / 113 (28.32%)
occurrences (all)	47	23	39
Malaise			
subjects affected / exposed	7 / 115 (6.09%)	7 / 78 (8.97%)	5 / 113 (4.42%)
occurrences (all)	8	7	6
Non-cardiac chest pain			
subjects affected / exposed	16 / 115 (13.91%)	11 / 78 (14.10%)	4 / 113 (3.54%)
occurrences (all)	22	15	4
Oedema peripheral			
subjects affected / exposed	6 / 115 (5.22%)	5 / 78 (6.41%)	11 / 113 (9.73%)
occurrences (all)	6	5	12
Pain			
subjects affected / exposed	8 / 115 (6.96%)	5 / 78 (6.41%)	2 / 113 (1.77%)
occurrences (all)	8	7	2
Pyrexia			
subjects affected / exposed	19 / 115 (16.52%)	14 / 78 (17.95%)	16 / 113 (14.16%)
occurrences (all)	32	25	25
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 115 (1.74%)	7 / 78 (8.97%)	4 / 113 (3.54%)
occurrences (all)	2	15	8

Oropharyngeal pain			
subjects affected / exposed	5 / 115 (4.35%)	4 / 78 (5.13%)	4 / 113 (3.54%)
occurrences (all)	5	4	4
Epistaxis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	6 / 113 (5.31%)
occurrences (all)	0	0	6
Dyspnoea			
subjects affected / exposed	18 / 115 (15.65%)	13 / 78 (16.67%)	18 / 113 (15.93%)
occurrences (all)	19	17	20
Cough			
subjects affected / exposed	20 / 115 (17.39%)	13 / 78 (16.67%)	20 / 113 (17.70%)
occurrences (all)	24	19	22
Rhinorrhoea			
subjects affected / exposed	2 / 115 (1.74%)	2 / 78 (2.56%)	6 / 113 (5.31%)
occurrences (all)	2	2	6
Productive cough			
subjects affected / exposed	7 / 115 (6.09%)	6 / 78 (7.69%)	7 / 113 (6.19%)
occurrences (all)	8	6	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 115 (9.57%)	6 / 78 (7.69%)	13 / 113 (11.50%)
occurrences (all)	13	6	13
Anxiety			
subjects affected / exposed	4 / 115 (3.48%)	7 / 78 (8.97%)	5 / 113 (4.42%)
occurrences (all)	4	8	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	52 / 115 (45.22%)	29 / 78 (37.18%)	10 / 113 (8.85%)
occurrences (all)	97	55	11
Amylase increased			
subjects affected / exposed	7 / 115 (6.09%)	5 / 78 (6.41%)	3 / 113 (2.65%)
occurrences (all)	20	7	3
Aspartate aminotransferase increased			
subjects affected / exposed	44 / 115 (38.26%)	25 / 78 (32.05%)	5 / 113 (4.42%)
occurrences (all)	76	51	6
Blood alkaline phosphatase increased			

subjects affected / exposed	28 / 115 (24.35%)	12 / 78 (15.38%)	1 / 113 (0.88%)
occurrences (all)	35	13	2
Blood creatinine increased			
subjects affected / exposed	24 / 115 (20.87%)	21 / 78 (26.92%)	1 / 113 (0.88%)
occurrences (all)	46	39	1
Electrocardiogram QT prolonged			
subjects affected / exposed	14 / 115 (12.17%)	8 / 78 (10.26%)	0 / 113 (0.00%)
occurrences (all)	25	14	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	27 / 115 (23.48%)	18 / 78 (23.08%)	3 / 113 (2.65%)
occurrences (all)	31	21	3
Lipase increased			
subjects affected / exposed	1 / 115 (0.87%)	5 / 78 (6.41%)	0 / 113 (0.00%)
occurrences (all)	9	8	0
Neutrophil count decreased			
subjects affected / exposed	1 / 115 (0.87%)	0 / 78 (0.00%)	8 / 113 (7.08%)
occurrences (all)	5	0	14
Weight decreased			
subjects affected / exposed	37 / 115 (32.17%)	13 / 78 (16.67%)	7 / 113 (6.19%)
occurrences (all)	42	13	7
White blood cell count decreased			
subjects affected / exposed	2 / 115 (1.74%)	0 / 78 (0.00%)	7 / 113 (6.19%)
occurrences (all)	4	0	9
Nervous system disorders			
Tremor			
subjects affected / exposed	6 / 115 (5.22%)	7 / 78 (8.97%)	0 / 113 (0.00%)
occurrences (all)	6	8	0
Somnolence			
subjects affected / exposed	5 / 115 (4.35%)	5 / 78 (6.41%)	3 / 113 (2.65%)
occurrences (all)	5	6	3
Paraesthesia			
subjects affected / exposed	3 / 115 (2.61%)	0 / 78 (0.00%)	6 / 113 (5.31%)
occurrences (all)	3	0	7
Neuropathy peripheral			

subjects affected / exposed	2 / 115 (1.74%)	1 / 78 (1.28%)	9 / 113 (7.96%)
occurrences (all)	3	1	9
Headache			
subjects affected / exposed	28 / 115 (24.35%)	16 / 78 (20.51%)	18 / 113 (15.93%)
occurrences (all)	43	20	21
Dizziness			
subjects affected / exposed	13 / 115 (11.30%)	10 / 78 (12.82%)	8 / 113 (7.08%)
occurrences (all)	16	12	8
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 115 (2.61%)	6 / 78 (7.69%)	9 / 113 (7.96%)
occurrences (all)	5	8	17
Febrile neutropenia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 78 (0.00%)	6 / 113 (5.31%)
occurrences (all)	0	0	6
Anaemia			
subjects affected / exposed	7 / 115 (6.09%)	8 / 78 (10.26%)	20 / 113 (17.70%)
occurrences (all)	8	13	22
Neutropenia			
subjects affected / exposed	6 / 115 (5.22%)	6 / 78 (7.69%)	25 / 113 (22.12%)
occurrences (all)	11	6	34
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	29 / 115 (25.22%)	20 / 78 (25.64%)	10 / 113 (8.85%)
occurrences (all)	44	27	11
Nausea			
subjects affected / exposed	73 / 115 (63.48%)	46 / 78 (58.97%)	27 / 113 (23.89%)
occurrences (all)	119	72	40
Stomatitis			
subjects affected / exposed	8 / 115 (6.96%)	5 / 78 (6.41%)	15 / 113 (13.27%)
occurrences (all)	11	6	23
Vomiting			
subjects affected / exposed	61 / 115 (53.04%)	37 / 78 (47.44%)	9 / 113 (7.96%)
occurrences (all)	144	61	10
Dyspepsia			

subjects affected / exposed	6 / 115 (5.22%)	2 / 78 (2.56%)	1 / 113 (0.88%)
occurrences (all)	8	2	1
Diarrhoea			
subjects affected / exposed	84 / 115 (73.04%)	57 / 78 (73.08%)	21 / 113 (18.58%)
occurrences (all)	180	100	31
Constipation			
subjects affected / exposed	25 / 115 (21.74%)	20 / 78 (25.64%)	15 / 113 (13.27%)
occurrences (all)	35	24	26
Abdominal pain upper			
subjects affected / exposed	22 / 115 (19.13%)	11 / 78 (14.10%)	5 / 113 (4.42%)
occurrences (all)	26	15	5
Dysphagia			
subjects affected / exposed	3 / 115 (2.61%)	4 / 78 (5.13%)	3 / 113 (2.65%)
occurrences (all)	3	4	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	14 / 115 (12.17%)	6 / 78 (7.69%)	7 / 113 (6.19%)
occurrences (all)	15	8	8
Dry skin			
subjects affected / exposed	6 / 115 (5.22%)	4 / 78 (5.13%)	2 / 113 (1.77%)
occurrences (all)	7	5	2
Alopecia			
subjects affected / exposed	6 / 115 (5.22%)	2 / 78 (2.56%)	24 / 113 (21.24%)
occurrences (all)	6	2	24
Rash			
subjects affected / exposed	15 / 115 (13.04%)	15 / 78 (19.23%)	13 / 113 (11.50%)
occurrences (all)	20	18	16
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 115 (0.00%)	4 / 78 (5.13%)	2 / 113 (1.77%)
occurrences (all)	0	4	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	8 / 115 (6.96%)	4 / 78 (5.13%)	7 / 113 (6.19%)
occurrences (all)	10	5	7
Neck pain			

subjects affected / exposed	8 / 115 (6.96%)	1 / 78 (1.28%)	2 / 113 (1.77%)
occurrences (all)	10	1	2
Myalgia			
subjects affected / exposed	6 / 115 (5.22%)	6 / 78 (7.69%)	14 / 113 (12.39%)
occurrences (all)	6	8	16
Musculoskeletal chest pain			
subjects affected / exposed	11 / 115 (9.57%)	3 / 78 (3.85%)	4 / 113 (3.54%)
occurrences (all)	12	3	4
Arthralgia			
subjects affected / exposed	23 / 115 (20.00%)	13 / 78 (16.67%)	16 / 113 (14.16%)
occurrences (all)	31	15	21
Back pain			
subjects affected / exposed	27 / 115 (23.48%)	10 / 78 (12.82%)	9 / 113 (7.96%)
occurrences (all)	36	14	10
Muscular weakness			
subjects affected / exposed	4 / 115 (3.48%)	5 / 78 (6.41%)	5 / 113 (4.42%)
occurrences (all)	4	6	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 115 (3.48%)	4 / 78 (5.13%)	4 / 113 (3.54%)
occurrences (all)	9	6	5
Cystitis			
subjects affected / exposed	0 / 115 (0.00%)	4 / 78 (5.13%)	0 / 113 (0.00%)
occurrences (all)	0	4	0
Influenza			
subjects affected / exposed	7 / 115 (6.09%)	2 / 78 (2.56%)	1 / 113 (0.88%)
occurrences (all)	8	3	1
Nasopharyngitis			
subjects affected / exposed	13 / 115 (11.30%)	6 / 78 (7.69%)	2 / 113 (1.77%)
occurrences (all)	16	14	2
Oral candidiasis			
subjects affected / exposed	6 / 115 (5.22%)	1 / 78 (1.28%)	3 / 113 (2.65%)
occurrences (all)	7	1	3
Pneumonia			
subjects affected / exposed	6 / 115 (5.22%)	5 / 78 (6.41%)	1 / 113 (0.88%)
occurrences (all)	14	6	1

Respiratory tract infection			
subjects affected / exposed	7 / 115 (6.09%)	3 / 78 (3.85%)	1 / 113 (0.88%)
occurrences (all)	9	3	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 115 (2.61%)	5 / 78 (6.41%)	4 / 113 (3.54%)
occurrences (all)	4	6	4
Urinary tract infection			
subjects affected / exposed	1 / 115 (0.87%)	6 / 78 (7.69%)	4 / 113 (3.54%)
occurrences (all)	1	7	18
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	50 / 115 (43.48%)	25 / 78 (32.05%)	23 / 113 (20.35%)
occurrences (all)	62	27	24
Hyperglycaemia			
subjects affected / exposed	9 / 115 (7.83%)	5 / 78 (6.41%)	3 / 113 (2.65%)
occurrences (all)	12	5	3
Hypoalbuminaemia			
subjects affected / exposed	4 / 115 (3.48%)	5 / 78 (6.41%)	2 / 113 (1.77%)
occurrences (all)	5	5	2
Hypokalaemia			
subjects affected / exposed	12 / 115 (10.43%)	7 / 78 (8.97%)	1 / 113 (0.88%)
occurrences (all)	20	8	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2013	This protocol amendment was implemented to address the availability of new safety data, to amend the eligible study population, and to clarify sections of the protocol where additional guidance was required.
20 May 2014	This protocol amendment was implemented to expand the inclusion criteria to allow for one (as in the prior version of the protocol) or two prior regimens of cytotoxic chemotherapy (one regimen must have included a platinum doublet) for the treatment of locally advanced or metastatic ALK - positive NSCLC and to allow more than one course of prior crizotinib treatment. Additional amendment items included updated safety information and clarification of sections of the protocol where additional guidance was required; updated safety data in the protocol and associated Informed Consent Form (ICF) to be consistent with the Investigator's Brochure Edition 6 (release 27 November 2013).
23 April 2015	This protocol amendment was implemented to delete the requirement for patients randomized to the chemotherapy arm to wait 31 days before crossing over to the crizotinib treatment arm and provide guidance on ceritinib treatment initiation for crossover patients to allow patients to cross over earlier if eligible. The time window for crossover to ceritinib treatment arm was increased from 56 days to 84 days, to allow for resolution of any adverse events (AEs) to grade ≤ 1 (NCI-Common Terminology Criteria for Adverse Events [CTCAE] v 4.03). In addition, patients who had a World Health Organization (WHO) performance status above 2 or a history of interstitial lung disease or interstitial pneumonitis were not allowed to cross over. Removed "start of new anti-cancer therapy" as an allowable reason to stop collecting tumor assessments. Updated the protocol based on currently available safety data. Pancreatic enzyme elevations (lipase and/or amylase) occur in patients treated with ceritinib. Clinical data suggest that a small proportion (<1%) of patients treated with ceritinib can develop clinical pancreatitis, and the causal role of ceritinib in these cases cannot be excluded. Due to this finding, the protocol was amended to include additional eligibility criteria, dose modification, and follow-up monitoring language for patients who may have experienced this safety finding. Added an evaluation of the anticipated benefits and risks to comply with European Union (EU) clinical trial regulations. Included an additional condition for the final analysis of PFS, requiring that all randomized patients completed at least 12 weeks of follow-up or had discontinued earlier.
11 December 2015	This protocol amendment was implemented to provide follow-up evaluations for hepatic toxicities and work-up guidelines for potential drug-induced liver injury (DILI) cases in order to optimize patient safety. Other changes: Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure. The secondary objectives and related endpoints were updated to specify that assessment of the antitumor activity of ceritinib versus reference chemotherapy in the brain, as measured by OIRR, IDCR and DOIR, would be as assessed by BIRC neuro-radiologist per modified RECIST 1.1 to allow selecting up to 5 measurable brain lesions as target lesions. In addition, already present information was clarified, where required.

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 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: