Clinical trial results:
A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer

Summary

EudraCT number	2012-003474-36
Trial protocol	IT ES GB SE DE NO BE
Global end of trial date	22 January 2018

Results information

Result version number	v1 (current)
This version publication date	07 February 2019
First version publication date	07 February 2019

Trial information

Trial identification

Sponsor protocol code	CLDK378A2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01685138
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Parma, 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	22 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antitumor activity of ceritinib, as measured by overall response rate (ORR) by Investigator assessment.

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	20 December 2012
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	France: 1
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	124
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	94
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 105 patients were planned to be enrolled. A total of 124 patients were enrolled and treated with ceritinib.

Pre-assignment

Screening details:

Approximately 105 patients were planned to be enrolled. A total of 124 patients were enrolled and treated with ceritinib.

Period 1

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

Arms

Arm title	LDK378 (Ceritinib)

Arm description:

Participants on this arm took oral LDK378 750 mg once daily.

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/LDK378 was supplied as 150 mg hard gelatin capsules and administered orally, once-daily at a dose of 750 mg on a continuous dosing schedule (5 x 150 mg capsules).

Number of subjects in period 1	LDK378 (Ceritinib)
Started	124
Discontinued from treatment phase	124
Entered post-treatment efficacy f/up	10 [1]
Entered survival follow-up	63
Discontinued from study	51
Completed	32
Not completed	92
Adverse event, serious fatal	10
Physician decision	6
Adverse event, non-fatal	18
Lost to follow-up	1
Progressive disease	53
No longer requires treatment	1

Subject/guardian decision	2
Protocol deviation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects dropped off at various time points during the course of the study.

Baseline characteristics

Reporting groups	
Reporting group title	LDK378 (Ceritinib)
Reporting group description:	
Participants on this arm took oral LDK378 750 mg once daily.	

Reporting group values	LDK378 (Ceritinib)	Total	
Number of subjects	124	124	
Age categorical Units: Subjects			
Adults (18-64 years)	94	94	
From 65-84 years	30	30	
Age Continuous Units: Years			
arithmetic mean	54.8		
standard deviation	± 12.16	-	
Sex: Female, Male Units: Subjects			
Female	74	74	
Male	50	50	
Race/Ethnicity, Customized Units: Subjects			
Asian	74	74	
Caucasian	48	48	
Black	1	1	
Other	1	1	

End points

End points reporting groups

Reporting group title	LDK378 (Ceritinib)

Reporting group description:

Participants on this arm took oral LDK378 750 mg once daily.

Primary: Overall response rate (ORR) by Investigator assessment

End point title	Overall response rate (ORR) by Investigator assessment[1]

End point description:

ORR per RECIST 1.1 calculated as the percentage of participants with a best overall response (BOR) defined as complete response (CR) or partial response (PR) as assessed by the investigator. 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	Primary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Percentage of participants				
number (confidence interval 95%)	67.7 (58.8 to 75.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR by Blinded Independent Review Committee (BIRC)

End point title	ORR by Blinded Independent Review Committee (BIRC)

End point description:

ORR per RECIST 1.1 calculated as the percentage of participants with a best overall response (BOR) defined as complete response (CR) or partial response (PR) as assessed by the BIRC. 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:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Percentage of participants				
number (confidence interval 95%)	63.7 (54.6 to 72.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) as per Investigator

End point title	Duration of response (DOR) as per Investigator

End point description:

DOR, calculated as the time from the date of the first documented CR or PR to the first documented progression or death due to any cause, 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:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	24.0 (14.8 to 37.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) as per BIRC

End point title	Duration of response (DOR) as per BIRC

End point description:

DOR, calculated as the time from the date of the first documented CR or PR to the first documented progression or death due to any cause, by BIRC 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. Discontinuation: permanent discontinuation of study drug for patients who experienced progressive disease (PD), or until PD was assessed by investigator if patients discontinued in the absence of PD.

End point type	Secondary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	27.3 (16.6 to 44.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) as per Investigator and BIRC

End point title	Disease Control Rate (DCR) as per Investigator and BIRC

End point description:

DCR per RECIST 1.1 is percentage of participants with best overall response of CR, PR, stable disease (SD) or Non-CR/Non-PD as per Investigator and BIRC. CR: Disappearance of all non-nodal target lesions. Also, 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. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions that would qualify for PD. PD: At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.

End point type	Secondary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Percentage of participants				
number (confidence interval 95%)				
DCR per Investigator	90.3 (83.7 to 94.9)			
DCR per BIRC	86.3 (79.0 to 91.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) as per Investigator

End point title	Time to Response (TTR) as per Investigator

End point description:

TTR, calculated as the time from first dose of LDK378 to first documented response (CR+PR), by investigator assessment. This was only on participants with confirmed CR or PR. 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:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
arithmetic mean (standard deviation)	2.5 (± 2.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) as per BIRC

End point title	Time to Response (TTR) as per BIRC

End point description:

TTR, calculated as the time from first dose of LDK378 to first documented response (CR+PR), by BIRC assessment. This was only on participants with confirmed CR or PR. 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:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
arithmetic mean (standard deviation)	2.2 (± 1.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall intracranial response rate (OIRR) as per Investigator

End point title	Overall intracranial response rate (OIRR) as per Investigator

End point description:

OIRR calculated as the ORR (CR+PR) of lesions in the brain for patients who have measureable disease in the brain at baseline by investigator.

End point type	Secondary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (confidence interval 95%)	20.0 (2.5 to 55.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall intracranial response rate (OIRR) as per BIRC

End point title	Overall intracranial response rate (OIRR) as per BIRC

End point description:

OIRR calculated as the ORR (CR+PR) of lesions in the brain for patients who have measureable disease in the brain at baseline by BIRC.

End point type	Secondary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage of participants				
number (confidence interval 95%)	61.5 (31.6 to 86.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) as per Investigator and BIRC

End point title	Progression-free survival (PFS) as per Investigator and BIRC

End point description:

PFS, defined as time from first dose of LDK378 to progression or death due to any cause, as assessed by investigator and BIRC assessment

End point type	Secondary

End point timeframe:

every 8 weeks (i.e. every 2 cycles; cycle = 28 days), starting from the first day of treatment with LDK378 until permanent discontinuation of study drug

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
median (confidence interval 95%)				
PFS per Investigator	16.6 (11.0 to 23.2)			
PFS per BIRC	19.4 (10.9 to 29.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS, defined as time from first dose of LDK378 to death due to any cause

End point type	Secondary

End point timeframe:

Time from the date of first dose of LDK378 to the date of death due to any cause up to 5 years

End point values	LDK378 (Ceritinib)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Months				
median (confidence interval 95%)	51.3 (42.7 to 55.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

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	20.1

Reporting groups

Reporting group title	LDK378 750 mg

Reporting group description:

LDK378 750 mg

Serious adverse events	LDK378 750 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 124 (40.32%)		
number of deaths (all causes)	56		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chordoma			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Asthenia				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	3 / 124 (2.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumonia aspiration				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumothorax				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation oesophagitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheal haemorrhage			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			

subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericarditis				
subjects affected / exposed	4 / 124 (3.23%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	2 / 124 (1.61%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Cognitive disorder				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	3 / 124 (2.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Headache				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures				

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radicular pain			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 124 (1.61%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal inflammation			

subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	5 / 124 (4.03%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 124 (2.42%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatitis				

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	2 / 124 (1.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	2 / 124 (1.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Bronchitis				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	4 / 124 (3.23%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Nosocomial infection				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parvovirus infection				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 124 (4.03%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketosis			

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	3 / 124 (2.42%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LDK378 750 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 124 (99.19%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	65 / 124 (52.42%)		
occurrences (all)	144		
Amylase increased			
subjects affected / exposed	14 / 124 (11.29%)		
occurrences (all)	20		
Aspartate aminotransferase increased			
subjects affected / exposed	58 / 124 (46.77%)		
occurrences (all)	105		
Blood alkaline phosphatase increased			
subjects affected / exposed	29 / 124 (23.39%)		
occurrences (all)	34		
Blood creatinine increased			
subjects affected / exposed	33 / 124 (26.61%)		
occurrences (all)	67		
Creatinine renal clearance decreased			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	13		
Electrocardiogram QT prolonged			
subjects affected / exposed	20 / 124 (16.13%)		
occurrences (all)	44		

Gamma-glutamyltransferase increased			
subjects affected / exposed	36 / 124 (29.03%)		
occurrences (all)	49		
Lipase increased			
subjects affected / exposed	9 / 124 (7.26%)		
occurrences (all)	16		
Weight decreased			
subjects affected / exposed	47 / 124 (37.90%)		
occurrences (all)	58		
Weight increased			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	8		
White blood cell count decreased			
subjects affected / exposed	9 / 124 (7.26%)		
occurrences (all)	16		
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 124 (16.94%)		
occurrences (all)	28		
Headache			
subjects affected / exposed	31 / 124 (25.00%)		
occurrences (all)	52		
Paraesthesia			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 124 (10.48%)		
occurrences (all)	18		
Neutropenia			
subjects affected / exposed	11 / 124 (8.87%)		
occurrences (all)	23		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 124 (15.32%)		
occurrences (all)	27		

Chest discomfort				
subjects affected / exposed	9 / 124 (7.26%)			
occurrences (all)	12			
Fatigue				
subjects affected / exposed	47 / 124 (37.90%)			
occurrences (all)	69			
Malaise				
subjects affected / exposed	9 / 124 (7.26%)			
occurrences (all)	14			
Non-cardiac chest pain				
subjects affected / exposed	19 / 124 (15.32%)			
occurrences (all)	25			
Pyrexia				
subjects affected / exposed	23 / 124 (18.55%)			
occurrences (all)	38			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	7 / 124 (5.65%)			
occurrences (all)	8			
Abdominal pain				
subjects affected / exposed	51 / 124 (41.13%)			
occurrences (all)	73			
Abdominal pain upper				
subjects affected / exposed	19 / 124 (15.32%)			
occurrences (all)	23			
Constipation				
subjects affected / exposed	35 / 124 (28.23%)			
occurrences (all)	42			
Diarrhoea				
subjects affected / exposed	106 / 124 (85.48%)			
occurrences (all)	370			
Dyspepsia				
subjects affected / exposed	15 / 124 (12.10%)			
occurrences (all)	16			
Gastrointestinal pain				

subjects affected / exposed	9 / 124 (7.26%)		
occurrences (all)	14		
Haemorrhoids			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	97 / 124 (78.23%)		
occurrences (all)	163		
Stomatitis			
subjects affected / exposed	14 / 124 (11.29%)		
occurrences (all)	16		
Vomiting			
subjects affected / exposed	89 / 124 (71.77%)		
occurrences (all)	199		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 124 (23.39%)		
occurrences (all)	50		
Dyspnoea			
subjects affected / exposed	31 / 124 (25.00%)		
occurrences (all)	40		
Oropharyngeal pain			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	11		
Productive cough			
subjects affected / exposed	15 / 124 (12.10%)		
occurrences (all)	24		
Rhinorrhoea			
subjects affected / exposed	9 / 124 (7.26%)		
occurrences (all)	16		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 124 (9.68%)		
occurrences (all)	12		
Pruritus			

subjects affected / exposed	18 / 124 (14.52%)		
occurrences (all)	25		
Rash			
subjects affected / exposed	28 / 124 (22.58%)		
occurrences (all)	37		
Rash maculo-papular			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	8		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 124 (8.87%)		
occurrences (all)	12		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 124 (20.16%)		
occurrences (all)	32		
Back pain			
subjects affected / exposed	32 / 124 (25.81%)		
occurrences (all)	37		
Bone pain			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	7		
Muscular weakness			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	21 / 124 (16.94%)		
occurrences (all)	25		
Myalgia			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	11		
Neck pain			

subjects affected / exposed	9 / 124 (7.26%)		
occurrences (all)	9		
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	18 / 124 (14.52%)		
occurrences (all)	30		
Pneumonia			
subjects affected / exposed	8 / 124 (6.45%)		
occurrences (all)	11		
Upper respiratory tract infection			
subjects affected / exposed	25 / 124 (20.16%)		
occurrences (all)	41		
Urinary tract infection			
subjects affected / exposed	10 / 124 (8.06%)		
occurrences (all)	29		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	69 / 124 (55.65%)		
occurrences (all)	117		
Hyperglycaemia			
subjects affected / exposed	15 / 124 (12.10%)		
occurrences (all)	20		
Hyperkalaemia			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	10		
Hypokalaemia			
subjects affected / exposed	14 / 124 (11.29%)		
occurrences (all)	28		
Hyponatraemia			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences (all)	10		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	9 / 124 (7.26%) 21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2013	At the time this amendment was issued 5 patients had been screened for enrollment and 3 patients had been treated with ceritinib. The amendment reflected the availability of new toxicity data, addressed requests from health authorities, and clarified sections of the protocol where additional guidance was required: •Addition of an ECG assessment for all patients 6 hours after first dose •Provided general guidance on dose modification •Provided guidance on dose modification in response to QTc prolongation •Provided guidance for treatment of hypophosphatemia •Clarified tumor sample collection requirements
27 August 2013	At the time this amendment was issued 57 patients had been screened for enrollment and 45 patients had been treated with ceritinib. The amendment addressed the availability of new safety data as represented in the latest Investigator Brochure and clarified sections of the protocol where additional guidance was required: •Addition of a secondary endpoint of OIRR for patients with measurable brain lesions at baseline to conduct a preliminary assessment of ceritinib activity in the brain. •Allowing pre-screening during prior chemotherapy treatment and prior to progression of disease. •Allowing the enrolment of chemotherapy-naive patients to target the ALK-inhibitors-naive population regardless of previous chemotherapy. •Update of safety data in the protocol and associated ICF to match the Investigator Brochure Edition 4 (released on 28-Jun-2013). •An exclusion criterion for patients with pneumonitis was added. Further, dose-modification criteria were added for patients who experience pneumonitis during the course of the study. •The definition of DOR was changed from time from first documented response (PR or CR) to the date of first documented disease progression or death due to underlying cancer to time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. The change, was done due to a request from the FDA and is further justifiable given that in an advanced cancer study it is difficult to ascertain whether a death is due to underlying cancer.
26 May 2015	As of the release date of this amendment, the recruitment had been completed. One hundred and thirty two patients were screened and 124 patients were treated with ceritinib. This amendment was implemented to include availability of new safety data as presented in the Investigator's Brochure and to clarify sections of the protocol where additional guidance was required: •Updated safety data in the protocol to match the Investigator's Brochure Edition 7 (released on 12-Jun-2014). The associated Informed Consent Form (ICF) was also updated separately to this protocol •Ceritinib dose modification and follow up of toxicities guidance was updated to handle elevations of pancreatic enzymes (lipase and/or amylase) based on available safety data.Pancreatic enzyme elevations (lipase and/or amylase) occurred in patients treated with ceritinib. Clinical data suggested that a small proportion (<1%) of patients treated with ceritinib could develop clinical pancreatitis, and the causal role of ceritinib in these cases couldn't be ruled out. The protocol was amended to include additional dose modification and follow up monitoring language for patients who may experience this event. •An evaluation of the anticipated benefits and risks were added to the protocol to comply with EU clinical trial regulations. •Sections related to study discontinuation were revised to bring clarification and provide additional guidance regarding study treatment discontinuation and withdrawal of consent.

11 December 2015	As of the release date of this amendment, the recruitment had been completed. In all, 132 patients were screened and 124 patients were treated with ceritinib. The amendment reflected the availability of new safety data, and updated sections of the protocol where additional guidance was required: •Protocol was updated to include follow up evaluations for hepatic toxicities and management guidelines for potential drug induced liver injury (DILI) cases in order to optimize patient safety. •Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure. •Updated the guidance related to corticosteroid use •Updated of the definition of the End of Study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported