Clinical trial results:
A Phase II, multi-center, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib.

Summary

EudraCT number	2012-003432-24
Trial protocol	ES GB NL IT DE BE FR
Global end of trial date	29 March 2016

Results information

Result version number	v1 (current)
This version publication date	12 April 2017
First version publication date	12 April 2017

Trial information

Trial identification

Sponsor protocol code	CLDK378A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01685060
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 Pharma, AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2016
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	26 November 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	Canada: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Japan: 24
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	140
EEA total number of subjects	57

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)	122
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 137 patients were planned to be enrolled. A total of 140 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 750mg

Arm description:

Patients treated with ceritinib/LDK378 750 mg once-daily, fasted.

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 were 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 750mg
Started	140
Entered post-treatment efficacy f/u	7
Entered survival follow up	98
Discontinued from study	35
Completed	0
Not completed	140
Physician decision	14
Adverse event, non-fatal	12
Death	8
Discontinuation due to study Completion	16
Progressive disease	69
Lost to follow-up	1
Subject/guardian decision	20

Baseline characteristics

Reporting groups	
Reporting group title	LDK378 750mg
Reporting group description:	
Patients treated with ceritinib/LDK378 750 mg once-daily, fasted.	

Reporting group values	LDK378 750mg	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	51.2		
standard deviation	± 11.62	-	
Gender, Male/Female Units: Subjects			
Female	70	70	
Male	70	70	

End points

End points reporting groups

Reporting group title	LDK378 750mg
Reporting group description:	
Patients treated with ceritinib/LDK378 750 mg once-daily, fasted.	

Primary: Overall response rate (ORR) to LDK378 per Investigator assessment

End point title	Overall response rate (ORR) to LDK378 per Investigator assessment[1]
End point description:	
ORR per RECIST 1.1 calculated as the percentage of patients with a best overall confirmed response defined as complete response or partial response (CR+PR) as assessed by 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 1. 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:	
6 cycles of 28 days up to 24 weeks	
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 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percentage of participants				
number (confidence interval 95%)	40.7 (32.5 to 49.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR per Blinded Independent Review Committee (BIRC) assessment

End point title	ORR per Blinded Independent Review Committee (BIRC) assessment
End point description:	
ORR (CR+PR) by BIRC is calculated as the percentage of patients with a best overall confirmed response defined as complete response or partial response (CR+PR) as assessed by 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 1. 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:	
6 cycles of 28 days up to 24 weeks	

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percentage of participants				
number (confidence interval 95%)	35.7 (27.8 to 44.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) by Investigator

End point title	Duration of response (DOR) by Investigator

End point description:

DOR, calculated as the time from the date of the first confirmed CR or PR to the first documented progression or death due to any cause, by 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 1. 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:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Months				
median (confidence interval 95%)	10.6 (7.4 to 14.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) by BIRC

End point title	Duration of response (DOR) by 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 underlying cancer, by BIRC (Blinded Imaging Review Committee). 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 1. 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:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Months				
median (confidence interval 95%)	12.9 (9.3 to 18.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

DCR was calculated as the percentage of patients with best overall response of CR, PR, SD, or non-CR non-PD (NCRNPD), per RECIST 1.1 by 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 1. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD. Non-CR/Non-PD (NCRNPD): refers to best overall responses that are neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percentage of participants				
number (confidence interval 95%)				
DCR per Investigator	76.4 (68.5 to 83.2)			
DCR per BIRC	80 (72.4 to 86.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) per Investigator

End point title	Time to Response (TTR) per Investigator

End point description:

TTR is the time from date of start of treatment to the first CR or PR observed which were confirmed afterwards.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
arithmetic mean (standard deviation)	3 (± 3.54)			

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 is the time from date of start of treatment to the first CR or PR observed which are confirmed afterwards.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Months				
arithmetic mean (standard deviation)	2.2 (± 1.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) per Investigator

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

End point description:

PFS, defined as the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient had no event or when the patient received any further anticancer therapy in the absence of disease progression, progression-free survival was censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: months				
median (confidence interval 95%)	5.8 (5.4 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) per BIRC

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

End point description:

PFS, defined as the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient had no event or when the patient received any further anticancer therapy in the absence of disease progression, progression-free survival was censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: months				
median (confidence interval 95%)	7.4 (5.6 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall intracranial response rate (OIRR) per Investigator

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

End point description:

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

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage of participants				
number (confidence interval 95%)	45 (23.1 to 68.5)			

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

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage of participants				
number (confidence interval 95%)	35.7 (18.6 to 55.9)			

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 the time from date of randomization/start of treatment to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last known date patient alive.

End point type	Secondary

End point timeframe:

6 cycles of 28 days up to 24 weeks

End point values	LDK378 750mg			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Months				
median (confidence interval 95%)	15.6 (13.6 to 24.2)			

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	18.1

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	67 / 140 (47.86%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
COLON CANCER			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METASTASES TO LIVER			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
METASTASES TO LUNG			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
METASTASES TO MENINGES			

subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
DISEASE PROGRESSION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
MALAISE			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
PAIN			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences causally related to treatment / all	2 / 11		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders				
COUGH				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	7 / 140 (5.00%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 2			
LUNG DISORDER				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PLEURAL EFFUSION				
subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
PLEURISY				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
PNEUMONITIS				
subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
PULMONARY HYPERTENSION				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
RESPIRATORY FAILURE				

subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Psychiatric disorders				
CONFUSIONAL STATE				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Investigations				
ALANINE AMINOTRANSFERASE INCREASED				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
ASPARTATE AMINOTRANSFERASE INCREASED				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
BLOOD CALCIUM INCREASED				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BLOOD CREATINE PHOSPHOKINASE INCREASED				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BLOOD CREATININE INCREASED				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
WEIGHT DECREASED				

subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
HUMERUS FRACTURE			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PUBIS FRACTURE			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PERICARDIAL EFFUSION			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
PERICARDITIS			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			

subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
APHASIA				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
BRAIN OEDEMA				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
DYSARTHRIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ENCEPHALOPATHY				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
HEADACHE				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HEPATIC ENCEPHALOPATHY				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HYPERAESTHESIA				

subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LETHARGY				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MOTOR DYSFUNCTION				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
PARAESTHESIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PARAPARESIS				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEIZURE				
subjects affected / exposed	4 / 140 (2.86%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
SENSORY LOSS				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood and lymphatic system disorders				
ANAEMIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				

subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
THROMBOCYTOPENIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
ASCITES				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DYSPHAGIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FAECALOMA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL DISORDER				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL TOXICITY				

subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL PERFORATION				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
NAUSEA				
subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				
subjects affected / exposed	2 / 140 (1.43%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
RETROPERITONEAL FIBROSIS				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	4 / 140 (2.86%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
HEPATIC FUNCTION ABNORMAL				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HEPATOCELLULAR INJURY				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

HYDRONEPHROSIS				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
POLLAKIURIA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RENAL FAILURE				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
RENAL IMPAIRMENT				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
BACK PAIN				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
BONE PAIN				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
NECK PAIN				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
EMPYEMA				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

ENTERITIS INFECTIOUS			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
LUNG INFECTION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
MENINGITIS			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
PLEURAL INFECTION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	6 / 140 (4.29%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	1 / 2		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEPTIC SHOCK			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIRAL PERICARDITIS			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
DEHYDRATION			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
DIABETES MELLITUS			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
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	139 / 140 (99.29%)		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	65 / 140 (46.43%)		
occurrences (all)	153		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	55 / 140 (39.29%)		
occurrences (all)	94		
BLOOD ALKALINE PHOSPHATASE			

INCREASED			
subjects affected / exposed	23 / 140 (16.43%)		
occurrences (all)	23		
BLOOD CREATININE INCREASED			
subjects affected / exposed	27 / 140 (19.29%)		
occurrences (all)	38		
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	15		
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	26 / 140 (18.57%)		
occurrences (all)	36		
WEIGHT DECREASED			
subjects affected / exposed	48 / 140 (34.29%)		
occurrences (all)	50		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	15 / 140 (10.71%)		
occurrences (all)	20		
DYSGEUSIA			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	12		
HEADACHE			
subjects affected / exposed	31 / 140 (22.14%)		
occurrences (all)	46		
PARAESTHESIA			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	25 / 140 (17.86%)		
occurrences (all)	29		
General disorders and administration site conditions			
ASTHENIA			

subjects affected / exposed	25 / 140 (17.86%)		
occurrences (all)	35		
FATIGUE			
subjects affected / exposed	54 / 140 (38.57%)		
occurrences (all)	67		
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	25 / 140 (17.86%)		
occurrences (all)	29		
OEDEMA PERIPHERAL			
subjects affected / exposed	19 / 140 (13.57%)		
occurrences (all)	22		
PYREXIA			
subjects affected / exposed	28 / 140 (20.00%)		
occurrences (all)	42		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	45 / 140 (32.14%)		
occurrences (all)	60		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	16 / 140 (11.43%)		
occurrences (all)	22		
CONSTIPATION			
subjects affected / exposed	42 / 140 (30.00%)		
occurrences (all)	52		
DIARRHOEA			
subjects affected / exposed	115 / 140 (82.14%)		
occurrences (all)	233		
NAUSEA			
subjects affected / exposed	115 / 140 (82.14%)		
occurrences (all)	225		
STOMATITIS			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	13		
VOMITING			
subjects affected / exposed	92 / 140 (65.71%)		
occurrences (all)	249		

Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	33 / 140 (23.57%)		
occurrences (all)	41		
DYSPNOEA			
subjects affected / exposed	29 / 140 (20.71%)		
occurrences (all)	30		
HAEMOPTYSIS			
subjects affected / exposed	10 / 140 (7.14%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	12		
DRY SKIN			
subjects affected / exposed	10 / 140 (7.14%)		
occurrences (all)	12		
PRURITUS			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	10		
RASH			
subjects affected / exposed	24 / 140 (17.14%)		
occurrences (all)	33		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	11		
INSOMNIA			
subjects affected / exposed	18 / 140 (12.86%)		
occurrences (all)	19		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 140 (11.43%)		
occurrences (all)	18		
BACK PAIN			

subjects affected / exposed occurrences (all) MUSCULOSKELETAL CHEST PAIN subjects affected / exposed occurrences (all) MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all) MYALGIA subjects affected / exposed occurrences (all) NECK PAIN subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	28 / 140 (20.00%) 34 9 / 140 (6.43%) 10 14 / 140 (10.00%) 14 10 / 140 (7.14%) 15 11 / 140 (7.86%) 12 14 / 140 (10.00%) 17		
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all) PNEUMONIA subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	 9 / 140 (6.43%) 14 9 / 140 (6.43%) 9 18 / 140 (12.86%) 36		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all) HYPOPHOSPHATAEMIA	 59 / 140 (42.14%) 77 8 / 140 (5.71%) 12		

subjects affected / exposed occurrences (all)	9 / 140 (6.43%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2013	The amendment reflected the availability of new safety 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 six hours after the first dose; Provided general guidance on dose modifications; Provided guidance on dose modifications in response to QTc prolongation; Provided guidance for treatment of hypophosphatemia; Clarified tumor sample collection requirements.
27 August 2013	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 overall intracranial response rate (OIRR) for patients with measurable brain lesions at baseline to conduct a preliminary assessment of ceritinib activity in the brain; 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 experienced pneumonitis during the course of the study; The definition of duration of response (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'. This change was made 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.
05 May 2015	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: Update of safety data in the protocol and associated ICF to match the Investigator Brochure Edition 7 (released on 12-Jun-2014); Update of ceritinib dose modification and follow-up toxicities in case of elevations of pancreatic enzymes (lipase and/or amylase); An evaluation of benefits and risks to comply with the EU clinical trial regulations; Update of the definition of end of study to take in to account of the availability of a rollover protocol; Reduced the frequency of tumor assessments to every 12 weeks from eight weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported