Clinical trial results:
An Open-Label, Non-Randomized, Multicenter Phase I/II Trial of RO5424802 Given Orally to Non-Small Cell Lung Cancer Patients Who have ALK Mutation and Who have Failed Crizotinib Treatment

Summary

EudraCT number	2012-004455-36
Trial protocol	SE GB DE IT ES NL BE FR DK LU
Global end of trial date	27 October 2017

Results information

Result version number	v2 (current)
This version publication date	17 October 2018
First version publication date	16 March 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NP28673

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01801111
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	27 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives for Part 1 of the study were:
To determine the recommended Phase 2 dose (RP2D) of alectinib (RO5424802) to be used in Part 2 of the study; To evaluate the safety and tolerability of 600 milligrams (mg) and 900-mg doses of alectinib administered twice daily to participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have anaplastic lymphoma kinase (ALK) rearrangement and in whom prior crizotinib therapy has failed; To characterize dose-limiting toxicities (DLTs), if any, associated with alectinib after 21 days of treatment; and To characterize the pharmacokinetics (PK) of alectinib and metabolite(s).

The primary objective for Part 2 of the study was: To evaluate efficacy of alectinib by objective response rate (ORR) as per independent radiological review committee (IRC) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1) criteria in the overall population.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP). Approval from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. No modifications were made to the protocol after receipt of the IEC/IRB approval.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Luxembourg: 2
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	138
EEA total number of subjects	78

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)	124
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall study status was confirmed as completed. Here, 'study terminated by sponsor' in reason for study not completed means participants were transitioned to commercial supply of alectinib (where it was available) or transitioned to a roll-over study BO39694 (NCT03194893) where they continued to receive alectinib treatment.

Pre-assignment

Screening details:

Part 1 of study was planned to determine the RP2D of alectinib to be used in Part 2. During the conduct of Part 1 for this study, RP2D was confirmed in Study NP28761 (NCT01871805). Hence Part 1 participants were merged into Part 2. Part 3 was post-progression treatment period.

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	Alectinib

Arm description:

Participants received alectinib at a dose of 600 mg via capsule, orally, twice daily, continuously starting on Day 1 Cycle 1 (in 28-day cycles) until disease progression (PD), death, or withdrawal for any other reasons, whichever occurred first. After PD, participants were allowed to continue treatment with alectinib as per the discretion of the treating physician.

Arm type	Experimental
Investigational medicinal product name	Alectinib
Investigational medicinal product code	
Other name	RO5424802
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Alectinib was administered at a dose of 600 mg via capsule, orally, twice daily.

Number of subjects in period 1	Alectinib
Started	138
Completed	0
Not completed	138
Physician decision	5
Consent withdrawn by subject	4
Adverse Event	12
Death	8
Progressive Disease	81
Unspecified	1
Study Terminated by Sponsor	27

Baseline characteristics

Reporting groups	
Reporting group title	Alectinib
Reporting group description:	
Participants received alectinib at a dose of 600 mg via capsule, orally, twice daily, continuously starting on Day 1 Cycle 1 (in 28-day cycles) until disease progression (PD), death, or withdrawal for any other reasons, whichever occurred first. After PD, participants were allowed to continue treatment with alectinib as per the discretion of the treating physician.	

Reporting group values	Alectinib	Total	
Number of subjects	138	138	
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 51.5 ± 11.1	 -	
Gender, Male/Female Units: Subjects			
Female	77	77	
Male	61	61	

End points

End points reporting groups

Reporting group title	Alectinib

Reporting group description:

Participants received alectinib at a dose of 600 mg via capsule, orally, twice daily, continuously starting on Day 1 Cycle 1 (in 28-day cycles) until disease progression (PD), death, or withdrawal for any other reasons, whichever occurred first. After PD, participants were allowed to continue treatment with alectinib as per the discretion of the treating physician.

Primary: RP2D of Alectinib

End point title	RP2D of Alectinib[1]

End point description:

RP2D was to be determined based on the safety and tolerability profile of the study treatment.

End point type	Primary

End point timeframe:

Cycle 1 (up to 28 days)

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: Due to EudraCT database limitations it is not possible to add statistical analysis in a single arm study.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: milligrams				
arithmetic mean (standard deviation)	()			

Notes:

[2] - The endpoint was not analyzed in this study as the RP2D was confirmed in study NP28761 (NCT01871805)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with DLTs

End point title	Percentage of Participants with DLTs[3]

End point description:

DLTs were to be assessed based on the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.3 (NCI-CTCAE v4.3). DLTs: drug-related toxicities that meet any one of the following criteria: Grade 4 thrombocytopenia; Grade 3 thrombocytopenia with bleeding; Grade 4 neutropenia continuing for greater than or equal to (>/=) 7 consecutive days or neutropenic fever; Non-hematological toxicity of Grade 3 or higher; Adverse events that require interruption of treatment for a total of >/=7 days.

End point type	Primary

End point timeframe:

Cycle 1 (up to 28 days)

Notes:

[3] - 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: Due to EudraCT database limitations it is not possible to add statistical analysis in a single

arm study.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - The endpoint was not analyzed in this study as the RP2D was confirmed in study NP28761 (NCT01871805)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving Objective Response (Complete Response [CR] or Partial Response [PR]) as Assessed by IRC in Response Evaluable (RE) Population

End point title	Percentage of Participants Achieving Objective Response (Complete Response [CR] or Partial Response [PR]) as Assessed by IRC in Response Evaluable (RE) Population[5]

End point description:

Tumor response was assessed by IRC according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to less than (<) 10 millimeters (mm). PR was defined as >/=30 percent (%) decrease in the sum of diameters (SoD) of target lesions (taking as reference the baseline SoD). The 95% confidence interval (CI) was computed using Clopper-Pearson method. Analysis was performed on RE population (IRC), which included all participants with measurable disease at baseline according to the IRC, who had baseline tumor assessment and received at least one dose of alectinib.

End point type	Primary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

Notes:

[5] - 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: Due to EudraCT database limitations it is not possible to add statistical analysis in a single arm study.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: percentage of participants				
number (confidence interval 95%)	50.8 (41.62 to 59.98)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by IRC in Chemotherapy-Pretreated Participants

End point title	Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by IRC in Chemotherapy-Pretreated Participants[6]

End point description:

Tumor response was assessed by IRC according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR was defined as >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). The 95% CI was computed using Clopper-Pearson method. Analysis was performed on RE population (IRC) participants who received prior chemotherapy.

End point type	Primary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

Notes:

[6] - 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: Due to EudraCT database limitations it is not possible to add statistical analysis in a single arm study.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: percentage of participants				
number (confidence interval 95%)	44.8 (34.63 to 55.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by IRC in Chemotherapy-Naive Participants

End point title	Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by IRC in Chemotherapy-Naive Participants

End point description:

Tumor response was assessed by IRC according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR was defined as >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). Analysis was performed on RE population (IRC) participants who did not receive prior chemotherapy.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage of participants				
number (not applicable)	73.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by Investigator in RE Population

End point title	Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by Investigator in RE Population

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR was defined as >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). The 95% CI was computed using Clopper-Pearson method. Analysis was performed on RE population (Investigator), which included all participants with measurable disease at baseline according to the investigator, who had baseline tumor assessment and received at least one dose of alectinib.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (confidence interval 95%)	51.4 (42.80 to 60.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by Investigator in Chemotherapy-Pretreated Participants

End point title	Percentage of Participants Achieving Objective Response (CR or

	PR) as Assessed by Investigator in Chemotherapy-Pretreated Participants

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR was defined as >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). Analysis was performed on RE population (investigator) participants who received prior chemotherapy.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: percentage of participants				
number (not applicable)	50.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by Investigator in Chemotherapy-Naive Participants

End point title	Percentage of Participants Achieving Objective Response (CR or PR) as Assessed by Investigator in Chemotherapy-Naive Participants

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. Objective response was defined as percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR was defined as >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). Analysis was performed on RE population (investigator) participants who did not receive prior chemotherapy.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (not applicable)	57.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) as Assessed by IRC in RE Population

End point title	Duration of Response (DoR) as Assessed by IRC in RE Population

End point description:

DoR was defined as the time from the first observation of an objective tumor response (CR or PR) until first observation of progressive disease (PD) according to RECIST v1.1 or death from any cause. CR: disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR: >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). PD: >/=20% relative increase and >/=5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-target lesions. Duration of response was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Participants who did not progress or die after a confirmed objective response were censored at the date of their last tumor assessment.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	62[7]			
Units: months				
median (confidence interval 95%)	15.2 (11.2 to 24.9)			

Notes:

[7] - Analysis was performed on RE population (IRC) participants with documented objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PD as Assessed by IRC According to RECIST v1.1 or Death from Any Cause in Safety Population

End point title	Percentage of Participants with PD as Assessed by IRC According to RECIST v1.1 or Death from Any Cause in Safety Population

End point description:

According to RECIST v1.1, PD was defined as >/=20% relative increase and >/=5 mm of absolute

increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-target lesions. Analysis was performed on safety population, which included all participants who received at least one dose of alectinib.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (not applicable)	71.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as Assessed by IRC in Safety Population

End point title	Progression Free Survival (PFS) as Assessed by IRC in Safety Population

End point description:

PFS was defined as the time interval between the date of the first treatment and the date of PD or death from any cause, whichever occurred first. PD: >/=20% relative increase and >/=5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-target lesions. PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Participants who neither progressed nor died at the time of assessment or who were lost to follow-up were censored at the date of the last tumor assessment. Participants with no post-baseline assessments were censored at the date of first dose. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: months				
median (confidence interval 95%)	8.9 (5.6 to 12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died of Any Cause

End point title	Percentage of Participants Who Died of Any Cause

End point description:

Percentage of participants who died of any cause was reported. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline up to death from any cause (up to approximately 4 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (not applicable)	54.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of first treatment to the date of death, regardless of the cause of death. OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Participants who did not die were censored at the date last known to be alive. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline up to death from any cause (up to approximately 4 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: months				
median (confidence interval 95%)	29.2 (21.5 to 44.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving CR, PR or Stable Disease (SD) According to RECIST v1.1 in RE Population

End point title	Percentage of Participants Achieving CR, PR or Stable Disease (SD) According to RECIST v1.1 in RE Population

End point description:

The disease control rate (DCR) was defined as the percentage of participants achieving CR, PR, or SD that lasted for at least 16 weeks. Tumor response was assessed by the investigator and IRC according to RECIST v1.1. CR: disappearance of all target, non-target lesions; normalization of tumor marker level; and reduction in all lymph nodes size to <10 mm. PR: >/=30% decrease in the SoD of target lesions (taking as reference the baseline SoD). PD: >/=20% relative increase and >/=5 mm of absolute increase in the SoD, taking as reference the smallest SoD recorded since treatment started; 1 or more new lesion(s); and/or unequivocal progression of non-target lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD while on study. The 95% CI was computed using Clopper-Pearson method. RE population: All participants who had baseline tumor assessment and received at least one dose of alectinib.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138[8]			
Units: percentage of participants				
number (confidence interval 95%)				
IRC Assessment (n=122)	63.9 (54.75 to 72.43)			
Investigator Assessment (n=138)	69.6 (61.16 to 77.11)			

Notes:

[8] - Here, 'n'=number of participant evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Central Nervous System (CNS) Objective Response as Assessed by IRC According to RECIST v1.1

End point title	Percentage of Participants Achieving Central Nervous System (CNS) Objective Response as Assessed by IRC According to RECIST v1.1

End point description:

CNS response was assessed by IRC according to RECIST v1.1. CNS Objective response was defined as percentage of participants with a CR or PR. CR was defined as disappearance of all CNS lesions. PR was defined as >/=30% decrease in the SoD of measurable CNS lesions (taking as reference the baseline SoD). The 95% CI was computed using Clopper-Pearson method. Analysis was performed on safety population participants with measurable CNS lesions at baseline.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)	58.8 (40.70 to 75.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving CNS Objective Response as Assessed by IRC According to Radiology Assessment in Neuro-Oncology (RANO) Criteria

End point title	Percentage of Participants Achieving CNS Objective Response as Assessed by IRC According to Radiology Assessment in Neuro-Oncology (RANO) Criteria

End point description:

CNS response was assessed by IRC according to RANO criteria. CNS Objective response: percentage of participants with a CR or PR that was confirmed by repeat assessments >/=4 weeks after initial documentation. CR was defined as complete disappearance of all enhancing measurable, non-measurable disease; stable or improved non-enhancing lesions; no new lesions; no corticosteroids (or only physiologic replacement dose), and clinically stable or improved. PR was defined as >/=50% decrease compared to screening in the sum of the products of the diameters (SPD) of enhancing measurable lesions; no progression of non-measurable disease (enhancing and non-enhancing lesions); no new lesions; no corticosteroids (or only physiologic replacement dose), and clinically stable or improved. The 95% CI was computed using Clopper-Pearson method. Analysis was performed on safety population participants with measurable CNS lesions at baseline.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up until cutoff 18 August 2014 (up to approximately 53 weeks)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)	44.1 (27.19 to 62.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: CNS Duration of Response (CDoR) as Assessed by IRC According to RECIST v1.1

End point title	CNS Duration of Response (CDoR) as Assessed by IRC According to RECIST v1.1

End point description:

CDoR was defined as the time from first observation of a CNS objective response (CR or PR) until first observation of CNS progression as assessed by IRC according to RECIST v 1.1 or death from any cause. CR: disappearance of all CNS lesions. PR: >/=30% decrease in the SoD of measurable CNS lesions (taking as reference the baseline SoD). CNS progression: >/=20% increase in the SoD of measurable CNS lesions (with an absolute increase of at least 5 mm), taking as reference the baseline SoD; 1 or more new CNS lesion(s); and/or unequivocal progression of non-measurable CNS lesions. CDoR was estimated by Kaplan-Meier method and 95% CI was assessed using method of Brookmeyer and Crowley. Analysis was performed on safety population participants with measurable CNS lesions at baseline and who had CNS objective response as assessed by IRC according to RECIST v1.1. Data '99999' in results signifies that upper limit of 95% CI could not be calculated due to high number of censored participants.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator, or last tumor assessment (up to approximately 2.5 years)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: months				
median (confidence interval 95%)	11.1 (7.1 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: CDoR as Assessed by IRC According to RANO Criteria

End point title	CDoR as Assessed by IRC According to RANO Criteria

End point description:

CDoR: time from the CNS objective response until CNS progression as assessed by IRC according to RANO criteria or death from any cause. CR: complete disappearance of all enhancing measurable, non-measurable disease; stable/improved non-enhancing lesions; no new lesions; no corticosteroids, and clinically stable/improved. PR: >/=50% decrease compared to screening in SPD of enhancing measurable lesions; no progression of non-measurable disease; no new lesions; no corticosteroids, and clinically stable/improved. Progression: >/=25% increase in SPD of enhancing measurable lesions compared to best response on study; stable/increasing doses of corticosteroids; significant increase in non-enhancing lesions not caused by co-morbid events; any new lesions; progression of non-measurable disease; or clinical deterioration not attributable to other non-tumor causes. CDoR was estimated by Kaplan-Meier method and 95% CI was assessed using method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up until cutoff 18 August 2014 (up to approximately 53 weeks)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	15[9]			
Units: months				
median (confidence interval 95%)	7.6 (7.4 to 7.6)			

Notes:

[9] - Safety population participants with measurable CNS lesions at baseline and CNS objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CNS Progression as Assessed by IRC According to RECIST v 1.1

End point title	Percentage of Participants with CNS Progression as Assessed by IRC According to RECIST v 1.1

End point description:

According to RECIST v 1.1, CNS progression was defined as >/=20% increase in the SoD of measurable CNS lesions (with an absolute increase of at least 5 mm), taking as reference the baseline SoD; 1 or more new CNS lesion(s); and/or unequivocal progression of non-measurable CNS lesions. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 weeks post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up until cutoff 18 August 2014 (up to approximately 53 weeks)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (not applicable)	18.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Alectinib

End point title	Maximum Observed Plasma Concentration (Cmax) of Alectinib

End point description:

Cmax for alectinib was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 (Pharsight Corporation) software. Analysis was performed on PK Evaluable Population, which included all participants who received any dose of alectinib and who had at least one post-baseline PK sample available. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours [hrs]), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	204 (± 47.6) 933 (± 34.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) of Alectinib

End point title	Time to Cmax (Tmax) of Alectinib

End point description:

Tmax for alectinib was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 software. Analysis was performed on PK Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs				
median (full range (min-max))				
Day 1 (n=28) Day 21 (n=26)	5.89 (2.00 to 10.00) 4.12 (0.0 to 11.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Plasma Concentration (Tlast) of Alectinib

End point title	Time to Last Measurable Plasma Concentration (Tlast) of Alectinib

End point description:

Tlast for alectinib was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 software.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	11.59 (± 3.9) 11.65 (± 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time 0 to 10 Hours Post-dose (AUC[0-10]) of Alectinib

End point title	Area Under the Plasma Concentration-Time Curve From Time 0 to 10 Hours Post-dose (AUC[0-10]) of Alectinib

End point description:

The AUC(0-10) of alectinib was calculated using the linear trapezoidal rule and actual sampling times (with the exception of pre-dose which was set to zero).

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs*nanograms per milliliter (hrs*ng/mL)				
geometric mean (geometric coefficient of variation)				

Day 1 (n=28) Day 21 (n=26)	1140 (± 44.5) 7860 (± 37.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time 0 to Tlast (AUC[0-last]) of Alectinib

End point title	Area Under the Plasma Concentration-Time Curve From Time 0 to Tlast (AUC[0-last]) of Alectinib

End point description:

The AUC(0-last) of alectinib was calculated using the linear trapezoidal rule and actual sampling times (with the exception of pre-dose which was set to zero).

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	1340 (± 44.9) 9090 (± 36.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Alectinib Metabolite

End point title	Cmax of Alectinib Metabolite

End point description:

Cmax for alectinib metabolite was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 software.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	57.2 (± 68.6) 303 (± 33.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Alectinib Metabolite

End point title	Tmax of Alectinib Metabolite

End point description:

Tmax for alectinib metabolite was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 software.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs				
median (full range (min-max))				
Day 1 (n=28) Day 21 (n=26)	8.03 (5.97 to 11.18) 7.00 (0.0 to 12.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast of Alectinib Metabolite

End point title	Tlast of Alectinib Metabolite

End point description:

Tlast for alectinib metabolite was estimated from plasma concentration versus time data by non-compartmental methods of analysis using Phoenix WinNonlin v6.2 software. Analysis was performed on PK Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28)	11.59 (± 3.9)			
Day 21 (n=26)	11.65 (± 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-10) of Alectinib Metabolite

End point title	AUC(0-10) of Alectinib Metabolite

End point description:

The AUC(0-10) of alectinib metabolite was calculated using the linear trapezoidal rule and actual sampling times (with the exception of pre-dose which was set to zero). Analysis was performed on PK Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28)	300 (± 68.4)			
Day 21 (n=26)	2590 (± 35.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-last) of Alectinib Metabolite

End point title	AUC(0-last) of Alectinib Metabolite

End point description:

The AUC(0-last) of alectinib metabolite was calculated using the linear trapezoidal rule and actual sampling times (with the exception of pre-dose which was set to zero). Analysis was performed on PK

Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hrs*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	378 (± 67.5) 3040 (± 34.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite to Parent Ratio Based on AUC(0-10)

End point title	Metabolite to Parent Ratio Based on AUC(0-10)

End point description:

Metabolite to parent ratio based on AUC(0-10) was computed as AUC(0-10) of metabolite divided by AUC(0-10) of parent drug (alectinib) corrected for the molecular weight of parent divided by the molecular weight of the metabolite. Analysis was performed on PK Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: no units				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	0.278 (± 41.0) 0.349 (± 28.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite to Parent Ratio Based on AUC(0-last)

End point title	Metabolite to Parent Ratio Based on AUC(0-last)

End point description:

Metabolite to parent ratio based on AUC(0-last) was computed as AUC(0-last) of metabolite divided by AUC(0-last) of parent drug (alectinib) corrected for the molecular weight of parent divided by the molecular weight of the metabolite. Analysis was performed on PK Evaluable Population. Here, 'n'=number of participant evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hrs post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: no units				
geometric mean (geometric coefficient of variation)				
Day 1 (n=28) Day 21 (n=26)	0.298 (± 41.2) 0.354 (± 28.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Alectinib

End point title	Trough Plasma Concentration (Ctrough) of Alectinib

End point description:

Analysis was performed on PK Evaluable Population. Here, 'Number of Subjects Analysed'=participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs) on Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	761 (± 42.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of Alectinib Metabolite

End point title	Ctrough of Alectinib Metabolite

End point description:

Analysis was performed on PK Evaluable Population. Here, 'Number of Subjects Analysed'=participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs) on Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	244 (± 37.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak to Trough Ratio of Alectinib

End point title	Peak to Trough Ratio of Alectinib

End point description:

Analysis was performed on PK Evaluable Population. Here, 'Number of Subjects Analysed'=participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose on Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Ratio (no units)				
geometric mean (geometric coefficient of variation)	1.23 (± 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio of Alectinib

End point title	Accumulation Ratio of Alectinib

End point description:

Accumulation ratio after repeat dosing was computed as AUC(0-10) on Day 21 divided by AUC(0-10) on Day 1. Analysis was performed on PK Evaluable Population. Here, 'Number of Subjects Analysed'=participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Ratio (no units)				
geometric mean (geometric coefficient of variation)	6.95 (± 42.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio of Alectinib Metabolite

End point title	Accumulation Ratio of Alectinib Metabolite

End point description:

Accumulation ratio after repeat dosing was computed as AUC(0-10) on Day 21 divided by AUC(0-10) on Day 1. Analysis was performed on PK Evaluable Population. Here, 'Number of Subjects Analysed'=participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (0 hrs), and 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose on Day 1 and Day 21 of Cycle 1

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Ratio (no units)				
geometric mean (geometric coefficient of variation)	8.68 (± 64.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until 28 days after the last dose of study drug (overall up to approximately 4 years)

Adverse event reporting additional description:

Analysis was performed on safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Alectinib

Reporting group description:

Participants received alectinib at a dose of 600 mg via capsule, orally, twice daily, continuously starting on Day 1 Cycle 1 (in 28-day cycles) until PD, death, or withdrawal for any other reasons, whichever occurred first. After PD, participants were allowed to continue treatment with alectinib as per the discretion of the treating physician.

Serious adverse events	Alectinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 138 (28.26%)		
number of deaths (all causes)	75		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic floor muscle weakness			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 138 (2.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Epistaxis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	3 / 138 (2.17%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	2 / 138 (1.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 138 (1.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 138 (1.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Head injury				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				

subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			

subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Oesophagitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterovesical fistula			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 138 (2.17%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Enterocolitis infectious			

subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 138 (0.72%)		
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	Alectinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 138 (96.38%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	30		
Asparatate aminotransferase increased			

subjects affected / exposed	18 / 138 (13.04%)		
occurrences (all)	28		
Blood bilirubin increased			
subjects affected / exposed	18 / 138 (13.04%)		
occurrences (all)	30		
Blood creatinine increased			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	9		
Weight increased			
subjects affected / exposed	18 / 138 (13.04%)		
occurrences (all)	18		
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	20		
Headache			
subjects affected / exposed	27 / 138 (19.57%)		
occurrences (all)	46		
Dysgeusia			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	7		
Paraesthesia			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 138 (13.77%)		
occurrences (all)	20		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	31 / 138 (22.46%)		
occurrences (all)	38		
Fatigue			
subjects affected / exposed	43 / 138 (31.16%)		
occurrences (all)	58		
Oedema			

subjects affected / exposed	9 / 138 (6.52%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	42 / 138 (30.43%)		
occurrences (all)	47		
Pyrexia			
subjects affected / exposed	17 / 138 (12.32%)		
occurrences (all)	18		
Chest pain			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	11		
Influenza like illness			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	11		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	25		
Abdominal pain upper			
subjects affected / exposed	17 / 138 (12.32%)		
occurrences (all)	22		
Constipation			
subjects affected / exposed	53 / 138 (38.41%)		
occurrences (all)	68		
Diarrhoea			
subjects affected / exposed	27 / 138 (19.57%)		
occurrences (all)	36		
Nausea			
subjects affected / exposed	32 / 138 (23.19%)		
occurrences (all)	39		
Vomiting			

subjects affected / exposed	22 / 138 (15.94%)		
occurrences (all)	28		
Dyspepsia			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 138 (23.19%)		
occurrences (all)	36		
Dyspnoea			
subjects affected / exposed	22 / 138 (15.94%)		
occurrences (all)	30		
Oropharyngeal pain			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	23		
Productive cough			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	15		
Dysphonia			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	11		
Dry skin			
subjects affected / exposed	13 / 138 (9.42%)		
occurrences (all)	18		
Photosensitivity reaction			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	18		
Rash			

subjects affected / exposed	24 / 138 (17.39%)		
occurrences (all)	29		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 138 (10.14%)		
occurrences (all)	19		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	22		
Back pain			
subjects affected / exposed	21 / 138 (15.22%)		
occurrences (all)	24		
Bone pain			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	9		
Muscular weakness			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	14 / 138 (10.14%)		
occurrences (all)	16		
Myalgia			
subjects affected / exposed	36 / 138 (26.09%)		
occurrences (all)	44		
Pain in extremity			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	20		
Muscle spasms			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	17		
Musculoskeletal chest pain			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	10		
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	21 / 138 (15.22%) 34		
Bronchitis subjects affected / exposed occurrences (all)	8 / 138 (5.80%) 14		
Influenza subjects affected / exposed occurrences (all)	7 / 138 (5.07%) 7		
Sinusitis subjects affected / exposed occurrences (all)	7 / 138 (5.07%) 7		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 138 (5.07%) 8		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	15 / 138 (10.87%) 25		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	17 / 138 (12.32%) 21		
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 138 (5.07%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	Exclusion criterion regarding use of anticoagulation or thrombolytic agent within 2 weeks prior to Day 1 was removed and timing for "archived primary tissue" was updated in the schedule of assessments.
28 May 2013	Serial PK sampling was included in Cycle 1 for the first 12 participants enrolled in Part 2 of the study; Dose reduction of 1-dose level was included for Grade 4 hematologic toxicity; Electrocardiograms were included to PK schedule, 2 hours after alectinib administration on Day 1 and Day 21 of Cycle 1; Action taken to detect an eventual QT/QTc prolongation were included; Description of potential phototoxicity and interstitial lung disease class effects and oxygen saturation were included to vital signs collection; It was clarified that the pregnancy test could be done any time during the study; The safety and efficacy data were updated; Total testosterone, free testosterone, follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH) testing was added; Collection of sample for the Roche Clinical Repository was removed; Completion/early termination sample collection was added; The reportable adverse events of special interest were updated; The schedule of assessments was updated for the PK/electrocardiogram schedule.
30 January 2014	A midazolam drug-drug interaction (DDI) sub-study was incorporated to be conducted in approximately 14 additional participants with ALK-positive NSCLC to gain critical information to support use of alectinib in combination with cytochrome P450 3A (CYP3A) substrates; Inclusion of Stage 3b NSCLC study participants was clarified; Post-progression combination treatment (alectinib and erlotinib) in Part 3 of the study was limited to participants with EGFR mutations and where local health authorities and ethic committees permitted it; The restriction for the last dose of crizotinib to be within 60 days from the first dose of alectinib was removed; The permitted and prohibited medications based on the available DDI information for alectinib was updated; The PK data was updated for study NP28761(NCT01871805); Eligibility for participants with brain or leptomeningeal metastases was clarified; The objectives and endpoints to assess alectinib efficacy on CNS lesions were clarified; tumor assessments during the long term follow-up visits were added; RANO criteria for IRC review of CNS lesions was included; The safety outcome measures with the addition of QTc assessment and the QTc analysis description were included; The safety section was updated with detailed guidance on management of selected adverse events.
14 April 2016	The summary of safety information for alectinib was updated to include newly available information; Recommendations for CYP3A and cytochrome P450 2C8 (CYP2C8) substrates and P-glycoprotein inhibitors were modified to reflect updated data; List of substrates, inhibitors, and inducers of drug metabolizing enzymes and transporters was updated; End of study was clarified.

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.

Part 1 analysis was not conducted as during the conduct of the study the RP2D was confirmed in study NP28761 (NCT01871805).

Notes: