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	

Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	16 March 2016

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, CH-4070, Basel, Switzerland,
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	Interim
Date of interim/final analysis	29 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: To determine the recommended Phase II Dose (RP2D) of alectinib to be used in Phase II of the study and to assess the safety, tolerability, and pharmacokinetic (PK) of alectinib 600 milligrams (mg) twice daily (BID) and 900 mg twice daily (BID) (if reached) dose regimens.

Part 2 and Part 3: To evaluate efficacy by objective response rate (ORR) as per independent radiological review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the overall population (with and without prior exposure of cytotoxic chemotherapy treatment[s]) and to evaluate efficacy by ORR as per IRC using RECIST version 1.1 in participants with prior exposure of cytotoxic chemotherapy treatment(s).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol.

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	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	Spain: 7
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Korea, Republic of: 17

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: -

Pre-assignment

Screening details:

Part 1 of study was planned to determine recommended Phase II Dose (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	Up to primary completion (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 600 mg, capsule, orally, BID, continuously starting on Cycle 1 (28-day cycle), Day 1 until disease progression, death, or withdrawal for any other reasons.

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

Dosage and administration details:

Alectinib 600 mg BID within 30 minutes after meals in the morning and evening.

Number of subjects in period 1	Alectinib
Started	138
Completed	0
Not completed	138
Treatment On-going	89
Death	24
On-going Survival Follow up	25

Baseline characteristics

Reporting groups	
Reporting group title	Alectinib
Reporting group description:	
Participants received alectinib 600 mg, capsule, orally, BID, continuously starting on Cycle 1 (28-day cycle), Day 1 until disease progression, death, or withdrawal for any other reasons.	

Reporting group values	Alectinib	Total	
Number of subjects	138	138	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	51.5		
standard deviation	± 11.1	-	
Gender categorical			
Units: Subjects			
Female	77	77	
Male	61	61	

End points

End points reporting groups

Reporting group title	Alectinib

Reporting group description:

Participants received alectinib 600 mg, capsule, orally, BID, continuously starting on Cycle 1 (28-day cycle), Day 1 until disease progression, death, or withdrawal for any other reasons.

Primary: Recommended Phase II Dose of Alectinib

End point title	Recommended Phase II Dose 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 tp 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: This endpoint was not analysed.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: mg				
number (not applicable)				

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 Dose Limiting Toxicities (DLTs)

End point title	Percentage of Participants With Dose Limiting Toxicities

End point description:

DLTs were to be assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.3. 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 ≥ 7 consecutive days or neutropenic fever; nonhematological 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: This endpoint was not analysed.

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 (NCT018718)

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Time Curve From Time 0 to 10 Hour Post-dose (AUC[0-10]) of Alectinib-Intensive PK Sampling

End point title	Area Under the Plasma Concentration Time Curve From Time 0 to 10 Hour Post-dose (AUC[0-10]) of Alectinib-Intensive PK Sampling[5]

End point description:

End point type	Primary

End point timeframe:

Day 1 and Day 21 of Cycle 1

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: This endpoint was not analysed.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: hour*nanogram per milliliter (hr*ng/mL)				
number (not applicable)				

Notes:

[6] - Data for this endpoint was not collected, as planned, because Part I of this study was not conducted

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 Independent Radiological Review Committee (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 Independent Radiological Review Committee (IRC) in Response Evaluable (RE) Population[7]

End point description:

Objective response was assessed by IRC according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 millimeter (mm). PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (IRC): 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 week post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up; data until cutoff (18 August 2014) are reported, maximum 53 weeks

Notes:

[7] - 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 formal statistical analysis was planned for this endpoint.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: percentage of participants				
number (confidence interval 95%)	49.2 (40.02 to 58.38)			

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[8]

End point description:

Objective response was assessed by IRC according to RECIST version. 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (IRC). Number of participants analyzed=participants from RE population (IRC) who received prior chemotherapy.

End point type	Primary

End point timeframe:

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

Notes:

[8] - 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 formal statistical analysis was planned for this endpoint.

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: percentage of participants				
number (confidence interval 95%)	43.8 (33.64 to 54.25)			

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:

Objective response was assessed by IRC according to RECIST version 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (IRC). Number of participants analyzed=participants from RE population (IRC) who did not receive prior chemotherapy.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage of participants				
number (confidence interval 95%)	69.2 (48.21 to 85.67)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Objective response was assessed by investigator according to RECIST version. 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (Investigator): 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 week post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up; data until cutoff (18 August 2014) are reported, maximum 53 weeks

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (confidence interval 95%)	47.8 (39.26 to 56.49)			

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:

Objective response was assessed by investigator according to RECIST version. 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (investigator). Number of participants analyzed=participants from RE population (investigator) who received prior chemotherapy.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: percentage of participants				
number (confidence interval 95%)	46.4 (36.8 to 56.12)			

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:

Objective response was assessed by investigator according to RECIST version. 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). CR and PR was to be confirmed by repeat assessments ≥4 weeks after initial documentation. Analysis was performed on RE population (investigator). Number of participants analyzed=participants from RE population (investigator) who did not receive prior chemotherapy.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (confidence interval 95%)	53.6 (33.87 to 72.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as time from first observation of objective tumor response until first observation of disease progression using RECIST version 1.1 or death from any cause. Duration of response was estimated by Kaplan-Meier method and 95% CI was assessed using method of Brookmeyer and Crowley. Duration of response was assessed by IRC and by investigator as well as in subgroups of participants who received prior chemotharapy and who did not received prior chemotherapy. Here, "99999" and "-99999" represents data was not mature at the time of analysis as the study was ongoing. Analysis was performed on RE population: participants with measurable disease at baseline, had baseline tumor assessment and received at least one dose of alectinib. Number of participants analyzed= participants with measurable disease at baseline and had objective response. n=participants with measurable disease at baseline and had objective response for specified category.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: months				
median (confidence interval 95%)				
All (IRC) (n=60)	9.2 (-99999 to 99999)			
Chemotherapy Pre-treated (IRC) (n=42)	9.2 (-99999 to 99999)			
Chemotherapy Naive (IRC) (n=18)	99999 (5.6 to 99999)			
All (Investigator) (n=66)	7.8 (7.4 to 9.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Progression or Death

End point title	Percentage of Participants With Progression or Death

End point description:

Progression (according to RECIST version 1.1) was defined as at least a 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study or absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesion. Progression was assessed by IRC and by the investigator in safety population as well as in subgroups of participants who received prior chemotharapy and who did not received prior chemotherapy. Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (not applicable)				
Safety population: IRC (n=138)	44.2			
Participants With Prior Chemotherapy: IRC (n=110)	46.4			
Chemotherapy-Naive Participants (n=28)	35.7			
Safety Population: Investigator (n=138)	41.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Baseline up to death or data cut off (18 August 2014, maximum follow up 53 weeks)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (not applicable)	17.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time interval between the date of the first treatment and the date of progression or death from any cause, whichever occurred first. Progression (according to RECIST version 1.1) was defined as at least a 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study or absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesion. Progression was assessed by IRC and by the investigator in safety population as well as in subgroups of participants who received prior chemotherapy and who did not received prior chemotherapy. PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Here "99999" represents data was not mature at the time of analysis as the study was ongoing. Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: months				
median (confidence interval 95%)				
Safety population: IRC (n=138)	7.5 (5.9 to 11.2)			
Participants With Prior Chemotherapy: IRC (n=110)	7.5 (5.6 to 11.2)			
Chemotherapy-Naive Participants:IRC (n=28)	99999 (5.5 to 99999)			
Safety Population: Investigator (n=138)	9.1 (7.4 to 11.2)			

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. Here "99999" represents data was not evaluable due to the short duration of follow-up at the time of the data cutoff. Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Baseline up to death or data cutoff (18 August 2014, maximum follow up 53 weeks)

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: months				
median (confidence interval 95%)	12.1 (12.1 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving CR, PR or Stable Disease (SD, Lasting ≥16 Weeks) in Response Evaluable Population

End point title	Percentage of Participants Achieving CR, PR or Stable Disease (SD, Lasting ≥16 Weeks) in Response Evaluable Population

End point description:

Disease control (CR, PR, or SD) was measured by RECIST version 1.1. by IRC and Investigator. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size is <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. Analysis was performed on RE population. Here, 'n' signifies participants with measurable disease at baseline for specified category.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (confidence interval 95%)				
RE population (IRC) (n=122)	63.9 (54.75 to 72.43)			
RE population (IRC) Prior therapy (n=96)	61.5 (50.97 to 71.22)			
RE population (IRC), Chemotherapy Naive (n=26)	73.1 (52.21 to 88.43)			
RE population (Investigator) (n=138)	68.8 (60.41 to 76.45)			
RE population (Investigator) Prior therapy(n=110)	69.1 (59.57 to 77.55)			
RE population (Investigator), therapy Naive(n=28)	67.9 (47.65 to 84.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Participants With CNS Response (CR or PR) as Assessed by IRC Based on RANO

End point title	Duration of Response in Participants With CNS Response (CR or PR) as Assessed by IRC Based on RANO

End point description:

Duration of response in participants with CNS response was defined as time from 1st observation of CNS response (CR or PR) until 1st observation of CNS progression or death from any cause based on IRC review of radiographs by RANO criteria. Progression was defined by any of following: ≥ 25% increase in sum of products of diameters of measurable enhancing lesions compared to best response after initiation of therapy (nadir), or screening if screening was nadir value on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR non-enhancing lesions not caused by co-morbid events on stable or increasing doses of corticosteroids; Any new lesions; Clear progression of enhancing non-measurable disease. Duration of response was estimated by Kaplan-Meier method and 95% CI was assessed using Brookmeyer and Crowley method. Clinical deterioration not attributable to other non-tumour causes. Participants with measurable CNS lesions at baseline according to IRC were included

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	7.6 (7.4 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Participants With CNS Response (CR or PR) as Assessed by IRC Based on RECIST

End point title	Duration of Response in Participants With CNS Response (CR or PR) as Assessed by IRC Based on RECIST

End point description:

Duration of response in participants with CNS response was defined as time from first observation of CNS response (CR or PR) until first observation of CNS progression or death from any cause based on IRC review of radiographs by RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions. PR was defined as ≥30% decrease in sum of diameters of target lesions (taking as reference screening sum diameters) and no progression of target lesions. Progression was defined as ≥20% increase in sum of diameters of target lesions compared to smallest sum of diameters on-study or absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesion. Duration of response was estimated by Kaplan-Meier method and 95% CI was assessed using method of Brookmeyer and Crowley. Analysis was performed on Safety population. Number of participants analyzed=participants with measurable CNS lesions at baseline according to IRC.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	7.6 (5.8 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response (CR or PR) of Baseline Central Nervous System (CNS) Lesions As Assessed by IRC Based on Radiology Assessment in Neuro-Oncology (RANO) Criteria

End point title	Percentage of Participants Achieving Objective Response (CR or PR) of Baseline Central Nervous System (CNS) Lesions As Assessed by IRC Based on Radiology Assessment in Neuro-Oncology (RANO) Criteria

End point description:

Objective response (CR and PR) of CNS lesions was assessed based on IRC review of radiographs by RANO criteria. CR was achieved if all of the following criteria met: Complete disappearance of all enhancing measurable and non-measurable disease; Stable or improved non-enhancing (T2/FLAIR) lesions; No new lesions; Participant must be off corticosteroids (or on physiologic replacement doses only), and clinically stable or improved. PR achieved if all of the following criteria met: at least 50% decrease compared with screening in SPD of measurable enhancing measurable lesions; No progression of non-measurable disease (enhancing and non-enhancing [T2/FLAIR] lesions); No new lesions; Participant must be off corticosteroids (or on physiologic replacement doses only), and clinically stable or improved. For both CR and PR, responses had to be sustained for at least 4 weeks. Safety population. Number of participants analyzed=participants with measurable CNS lesions at baseline according to IRC.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 week post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up; data until cutoff (18 August 2014) are reported, maximum 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: Percentage of Participants Achieving Objective Response (CR or PR) of Baseline Central Nervous System (CNS) Lesions As Assessed by IRC Based on RECIST

End point title	Percentage of Participants Achieving Objective Response (CR or PR) of Baseline Central Nervous System (CNS) Lesions As Assessed by IRC Based on RECIST

End point description:

Objective response (CR and PR) of CNS lesions was assessed based on IRC review of radiographs by RECIST version 1.1 in participants with measurable CNS lesions at baseline. CR was defined as disappearance of all target and non-target lesions. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the screening sum diameters) and no progression of target lesions. Analysis was performed on Safety population. Number of participants analyzed=participants measurable CNS lesions at baseline and who achieved a CNS response of CR or PR according to IRC.

End point type	Secondary

End point timeframe:

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

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)	55.9 (37.89 to 72.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CNS Progression As Assessed by IRC Based on RECIST

End point title	Percentage of Participants With CNS Progression As Assessed by IRC Based on RECIST

End point description:

CNS progression was defined as the percentage of participants who developed a new CNS lesion or have disease progression in pre-existing CNS lesions based on IRC review of radiographs by RECIST version 1.1. Progression was defined as at least 20% increase in the sum of diameters of target lesions compared to smallest sum of diameters on-study or absolute increase of at lease 5 mm, progression of existing non-target lesions, or presence of new lesion. Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Baseline; assessments every 8 week post-baseline until progressive disease, unacceptable toxicity, consent withdrawal, death, other reason deemed by investigator; then survival follow-up; data until cutoff (18 August 2014) are reported, maximum 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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to cut off (maximum 53 weeks of drug exposure)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Alectinib

Reporting group description:

Participants received alectinib 600 mg, capsule, orally, BID, continuously starting on Cycle 1 (28 day cycle), Day 1 until disease progression, death, or withdrawal for any other reasons.

Serious adverse events	Alectinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 138 (15.94%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events			
Investigations			
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		
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		
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		
Injury, poisoning and procedural complications			
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			
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			
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			
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			
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			
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	1 / 138 (0.72%)			
occurrences causally related to treatment / all	1 / 1			
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			
Hepatobiliary disorders				
Hyperbilirubinaemia				
subjects affected / exposed	2 / 138 (1.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
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			
Epistaxis				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 138 (1.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

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		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
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	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 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		
Sepsis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		

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		

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	126 / 138 (91.30%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	13 / 138 (9.42%)		
occurrences (all)	17		
Alanine aminotransferase increased			
subjects affected / exposed	13 / 138 (9.42%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	16		
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 138 (15.94%)		
occurrences (all)	24		
Dizziness			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	13		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	34 / 138 (24.64%)		
occurrences (all)	35		
Asthenia			
subjects affected / exposed	25 / 138 (18.12%)		
occurrences (all)	29		
Oedema			

subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	36 / 138 (26.09%)		
occurrences (all)	37		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 138 (9.42%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	14 / 138 (10.14%)		
occurrences (all)	17		
Constipation			
subjects affected / exposed	44 / 138 (31.88%)		
occurrences (all)	50		
Abdominal pain upper			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	14 / 138 (10.14%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	17		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 138 (13.77%)		
occurrences (all)	21		
Productive cough			

subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	18		
Oropharyngeal pain			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	18		
Dry skin			
subjects affected / exposed	9 / 138 (6.52%)		
occurrences (all)	10		
Photosensitivity reaction			
subjects affected / exposed	12 / 138 (8.70%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	9		
Myalgia			
subjects affected / exposed	31 / 138 (22.46%)		
occurrences (all)	41		
Muscular weakness			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	11		
Musculoskeletal pain			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	11		
Pain in extremity			

subjects affected / exposed	9 / 138 (6.52%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	12 / 138 (8.70%)		
occurrences (all)	12		
Arthralgia			
subjects affected / exposed	12 / 138 (8.70%)		
occurrences (all)	13		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 138 (7.25%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	This purpose of this amendment was to remove exclusion criterion regarding use of anticoagulation or thrombolytic agent within 2 weeks prior to Day 1.
28 May 2013	To consolidate the country-specific Health Authorities' requests that had been incorporated for Taiwan, Korea, Germany, France, United Kingdom, and Belgium. Addition of total testosterone, free testosterone, follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH) testing. Removal of collection of sample for the Roche Clinical Repository. Change in mandatory plasma sample collection: Addition of a completion/early termination sample. Update on the reportable adverse events of special interest. Update of the Schedule of Assessments, and PK/ECG schedule, in agreement with the changes made throughout the protocol.
19 November 2013	To modify specific inclusion and exclusion criteria for the midazolam sub study to allow enrolment of participants previously treated with any ALK inhibitor (approved or experimental). To clarify the possibility of using parenteral formulations of midazolam for oral administration.
30 January 2014	To limit post-progression combination treatment (alectinib and erlotinib) in Part 3 of the study for participants with EGFR mutations to countries in which local health authorities and ethic committees permit it, following a request of the Spanish Health authority. To remove the restriction for the last dose of crizotinib to be within 60 days from the first dose of alectinib. This restriction was first put in place to avoid possible re-sensitization to crizotinib and ensure that all participants are true crizotinib-failure. However, this limitation was thought to potentially affect enrollment as it may not have allowed enough time for participants to progress on subsequent chemotherapy treatments. To update the permitted and prohibited medications based on the available drug drug interaction (DDI) information for alectinib with the intent to maintain the critical DDI restrictions to support appropriate use of alectinib for participants receiving concomitant medications while ensuring patients were able to receive critical concomitant medications needed to treat comorbid conditions.

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 the during conduct of the study the RP2D was confirmed in study NP28761 (NCT01871805).

Notes: