Clinical trial results:
An Open-Label, Multicenter, Single-Arm, Phase II Study to Assess the Efficacy and Safety of Alectinib in Patients with ALK-Rearranged Non-Small Cell Lung Cancer After Disease Progression on Prior ALK Inhibitor Therapy

Summary

EudraCT number	2016-003924-22
Trial protocol	FR
Global end of trial date	26 September 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2020
First version publication date	04 October 2020

Trial information

Trial identification

Sponsor protocol code	ML39349

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03155009
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, 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	26 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of alectinib, in selected participants, with anaplastic lymphoma kinase-rearranged (ALK-rearranged) non-small cell lung cancer (NSCLC).

Protection of trial subjects:

All participants were required to sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2017
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	France: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	29
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with histologically or cytologically confirmed locally advanced or metastatic NSCLC (Stage IIIB or IV accordingly to American Joint Committee on Cancer [AJCC] classification)

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 with confirmed NSCLC received 600 mg of oral alectinib twice daily with food.

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

Dosage and administration details:

Participants received 600 mg by mouth twice daily.

Number of subjects in period 1	Alectinib
Started	44
Completed	21
Not completed	23
Consent withdrawn by subject	3
Adverse event, non-fatal	4
Death	6
Post-treatment visit not completed	2
Progression of disease	5
Reason not specified	3

Baseline characteristics

Reporting groups	
Reporting group title	Alectinib
Reporting group description:	
Participants with confirmed NSCLC received 600 mg of oral alectinib twice daily with food.	

Reporting group values	Alectinib	Total	
Number of subjects	44	44	
Age Categorical Units: Subjects			
Adults (18-64 years)	29	29	
From 65-84 years	15	15	
Age Continuous Units: years			
arithmetic mean	57.7		
standard deviation	± 13.6	-	
Gender Categorical Units: Subjects			
Female	19	19	
Male	25	25	

End points

End points reporting groups

Reporting group title	Alectinib

Reporting group description:

Participants with confirmed NSCLC received 600 mg of oral alectinib twice daily with food.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR is defined as the percentage of participants with complete response (CR) or partial response (PR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), v.1.1. CR is defined as disappearance of all target and non-target lesions and no new lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. PR is defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions.

End point type	Primary

End point timeframe:

Up to 2 years

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: Specified in the description. Additional information: ORR as per investigator will be descriptively summarized by the number and proportion of responders and non-responders, together with their two-sided 95% Confidence Intervals (exact CI computed using Clopper-Pearson method).

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (confidence interval 95%)				
Complete Response	10.3 (2.9 to 24.2)			
Partial Response	41.0 (25.6 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Central Nervous System Objective Response Rate (C-ORR)

End point title	Central Nervous System Objective Response Rate (C-ORR)

End point description:

C-ORR is defined as the percentage of participants who attain a CR or PR of the baseline CNS metastases based on RECIST v.1.1. CR is defined as disappearance of all target and non-target lesions and no new lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. PR is defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage of Participants				
number (confidence interval 95%)				
Complete Response	27.3 (6.0 to 61.0)			
Partial Response	63.6 (30.8 to 89.1)			

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 is defined as the time between first intake of alectinib and the first occurrence of disease progression, or death from any cause during the study, whichever occurs first. Progressive disease (PD) based on RECIST v.1.1. is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	44[2]			
Units: Months				
median (confidence interval 95%)	14.4 (9.2 to 9999)			

Notes:

[2] - 9999 = upper limit not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP is defined as the time between first intake of alectinib and the first occurrence of disease progression. PD based on RECIST v.1.1. is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	44[3]			
Units: Months				
median (confidence interval 95%)	14.9 (10.9 to 9999)			

Notes:

[3] - 9999 = upper limit not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

DCR is defined as the percentage of participants who attain CR, PR, or stable disease (SD) for at least five weeks, based on RECIST v.1.1. CR is defined as disappearance of all target and non-target lesions and no new lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. PR is defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression, taking as reference the smallest sum on study.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (confidence interval 95%)	94.9 (82.7 to 99.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the time from when response (CR or PR), based on RECIST v.1.1, will be first documented to first documented disease progression or death (whichever occurs first). CR is defined as disappearance of all target and non-target lesions and no new lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. PR is defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. DOR assessment is restricted to participants with a BOR of CR or PR.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	21[4]			
Units: Months				
median (confidence interval 95%)	9999 (9.2 to 9999)			

Notes:

[4] - 9999 = value not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Central Nervous System DOR (C-DOR)

End point title	Central Nervous System DOR (C-DOR)

End point description:

C-DOR is defined as the time from the first observation of a CNS response of CR or PR based on RECIST V1.1 until first observation of CNS progression or death from any cause (whichever occurs first). CR is defined as disappearance of all target and non-target lesions and no new lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. PR is defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. C-DOR assessment is restricted to those participants with measurable CNS metastases at baseline and with CNS BOR of CR or PR.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	10[5]			
Units: Months				
median (confidence interval 95%)	12.9 (2.0 to 9999)			

Notes:

[5] - 9999 = upper limit not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the percentage of participants alive two years after the start of treatment.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	44[6]			
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Notes:

[6] - 9999 = parameter not estimable due to lack of participants with event

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Central Nervous System (CNS) Progression (TTCP)

End point title	Time to Central Nervous System (CNS) Progression (TTCP)

End point description:

TTCP is defined as the time from first drug intake to first documented occurrence of disease progression in the CNS. PD based on RECIST v.1.1. is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	44[7]			
Units: Months				
median (confidence interval 95%)	9999 (14.9 to 9999)			

Notes:

[7] - 9999 = value not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)

End point description:

An adverse event is considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsen during the study are reported as adverse events.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Percentage of Participants				
number (not applicable)				
Non-emergent	27.3			
Emergent	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (QoL) as Assessed by the QLQ-C30 Questionnaire

End point title	Health-Related Quality of Life (QoL) as Assessed by the QLQ-C30 Questionnaire

End point description:

The QLQ-C30 Questionnaire is used to assess the quality of life of participants with cancer. It includes five functional scales, three symptom scales, a global health status / QoL scale, and six single items. These components range in score from 0 (low response level) to 100 (high response level).
This endpoint reports the average change from baseline for each domain.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	43[8]			
Units: Percentage				
number (not applicable)				
Global health status/QoL - Improvement	39.5			
Global health status/QoL - Stable	48.8			
Global health status/QoL - Worsening	11.6			
Physical Functioning (revised) score - Improvement	34.9			
Physical Functioning (revised) score - Stable	46.5			
Physical Functioning (revised) score - Worsening	18.6			
Role functioning (revised) - Improvement	48.8			
Role functioning (revised) - Stable	34.9			
Role functioning (revised) - Worsening	16.3			
Emotional functioning score - Improvement	41.9			
Emotional functioning score - Stable	44.2			
Emotional functioning score - Worsening	14.0			
Cognitive functioning score - Improvement	30.2			
Cognitive functioning score - Stable	53.5			
Cognitive functioning score - Worsening	16.3			
Social functioning score - Improvement	44.2			
Social functioning score - Stable	41.9			
Social functioning score - Worsening	14.0			
Fatigue score - Improvement	39.5			
Fatigue score - Stable	60.5			
Fatigue score - Worsening	20.9			
Nausea and vomiting score - Improvement	34.9			
Nausea and vomiting score - Stable	60.5			
Nausea and vomiting score - Worsening	4.7			
Pain score - Improvement	46.5			
Pain score - Stable	32.6			
Pain score - Worsening	20.9			
Dyspnoea score - Improvement	41.9			
Dyspnoea score - Stable	34.9			
Dyspnoea score - Worsening	23.3			
Insomnia score - Improvement	32.6			
Insomnia score - Stable	44.2			
Insomnia score - Worsening	23.3			
Appetite loss score - Improvement	34.9			
Appetite loss score - Stable	51.2			
Appetite loss score - Worsening	14.0			
Constipation score - Improvement	18.6			
Constipation score - Stable	48.8			

Constipation score - Worsening	32.6			
Diarrhoea - Improvement	34.9			
Diarrhoea - Stable	60.5			
Diarrhoea - Worsening	4.7			
Financial difficulties score - Improvement	18.6			
Financial difficulties score - Stable	67.4			
Financial difficulties score - Worsening	14.0			

Notes:

[8] - Global health status/QoL = revised scores

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related QoL as Assessed by the LC13 Questionnaire

End point title	Health-Related QoL as Assessed by the LC13 Questionnaire

End point description:

The LC13 Questionnaire includes 13 questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia), and pain medication. This scale ranges in score from 0 (low response level) to 100 (high response level).
This end point reports average change from baseline in each domain.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	43[9]			
Units: Percentage				
number (not applicable)				
Coughing score - Improvement	30.2			
Coughing score - Stable	48.8			
Coughing score - Worsening	20.9			
Haemoptysis score - Stable	97.7			
Haemoptysis score - Worsening	2.3			
Dyspnoea score - Improvement	30.2			
Dyspnoea score - Stable	46.5			
Dyspnoea score - Worsening	23.3			
Dyspnoea when resting score - Improvement	23.3			
Dyspnoea when resting score - Stable	60.5			
Dyspnoea when resting score - Worsening	16.3			
Dyspnoea when walking score - Improvement	27.9			
Dyspnoea when walking score - Stable	46.5			
Dyspnoea when walking score - Worsening	25.6			

Dyspnoea when stairs score - Improvement	41.9			
Dyspnoea when stairs score - Stable	27.9			
Dyspnoea when stairs score - Worsening	30.2			
Sore mouth score - Improvement	16.3			
Sore mouth score - Stable	74.4			
Sore mouth score - Worsening	9.3			
Dysphagia score - Improvement	20.9			
Dysphagia score - Stable	72.1			
Dysphagia score - Worsening	7.0			
Peripheral neuropathy score - Improvement	21.4			
Peripheral neuropathy score - Stable	64.3			
Peripheral neuropathy score - Worsening	14.3			
Alopecia score - Improvement	9.3			
Alopecia score - Stable	74.4			
Alopecia score - Worsening	16.3			
Pain in chest score - Improvement	25.6			
Pain in chest score - Stable	58.1			
Pain in chest score - Worsening	16.3			
Pain in arm or shoulder score - Improvement	25.6			
Pain in arm or shoulder score - Stable	32.6			
Pain in arm or shoulder score - Worsening	41.9			
Pain in other parts score - Improvement	41.5			
Pain in other parts score - Stable	34.1			
Pain in other parts score - Worsening	24.4			
Pain after relief medication score - Improvement	31.6			
Pain after relief medication score - Stable	34.1			
Pain after relief medication score - Worsening	15.8			

Notes:

[9] - N=41 for Pain in other parts
N=42 for Peripheral neuropathy
N=19 for Pain relief after medication

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related QoL as Assessed by the BN20 Questionnaire

End point title	Health-Related QoL as Assessed by the BN20 Questionnaire

End point description:

The BN20 Questionnaire includes 20 items assessing future uncertainty, visual disorder, motor dysfunction, communication deficit and other disease symptoms, and treatment toxicities. This scale ranges in score from 0 (low response level) to 100 (high response level).
This endpoint reports data for the average change from baseline for each domain.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Alectinib			
Subject group type	Reporting group			
Number of subjects analysed	43[10]			
Units: Percentage				
number (not applicable)				
Future uncertainty score - Improvement	59.5			
Future uncertainty score - Stable	31.0			
Future uncertainty score - Worsening	9.5			
Headaches score - Improvement	46.5			
Headaches score - Stable	39.5			
Headaches score - Worsening	14.0			
Visual disorder score - Improvement	27.9			
Visual disorder score - Stable	55.8			
Visual disorder score - Worsening	16.3			
Seizures score - Improvement	7.0			
Seizures score - Stable	88.4			
Seizures score - Worsening	4.7			
Motor dysfunction score - Improvement	31.0			
Motor dysfunction score - Stable	59.5			
Motor dysfunction score - Worsening	9.5			
Communication deficit score - Improvement	23.3			
Communication deficit score - Stable	67.4			
Communication deficit score - Worsening	9.3			
Drowsiness score - Improvement	32.6			
Drowsiness score - Stable	37.2			
Drowsiness score - Worsening	30.2			
Hair loss score - Improvement	16.3			
Hair loss score - Stable	74.4			
Hair loss score - Worsening	9.3			
Itchy skin score - Improvement	7.0			
Itchy skin score - Stable	72.1			
Itchy Skin score - Worsening	20.9			
Weakness of legs score - Improvement	20.9			
Weakness of legs score - Stable	58.1			
Weakness of legs score - Worsening	20.9			
Bladder control score - Improvement	16.3			
Bladder control score - Stable	58.1			
Bladder control score - Worsening	25.6			

Notes:

[10] - N=42 for Future uncertainty and for Motor dysfunction

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Approximately 2 years	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Alectinib
Reporting group description: Participants with confirmed NSCLC received 600 mg of oral alectinib twice daily with food.	

Serious adverse events	Alectinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 44 (22.73%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular dysfunction			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Epilepsy			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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	44 / 44 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 44 (29.55%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	13 / 44 (29.55%)		
occurrences (all)	13		
Non-cardiac chest pain			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	11		
Cough			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	10		
Pleural effusion			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Investigations			

Weight increased			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	11		
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Blood lactate dehydrogenase increase			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 44 (27.27%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 44 (22.73%)		
occurrences (all)	11		
Neutropenia			

subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 4 / 44 (9.09%) 5		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 16 / 44 (36.36%) 18 7 / 44 (15.91%) 7 5 / 44 (11.36%) 5 4 / 44 (9.09%) 4		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 2 / 44 (4.55%) 2		
Skin and subcutaneous tissue disorders Photosensitivity reaction subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	 5 / 44 (11.36%) 5 3 / 44 (6.82%) 4		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 3 / 44 (6.82%) 4		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	14 / 44 (31.82%) 14		
Arthralgia subjects affected / exposed occurrences (all)	8 / 44 (18.18%) 8		
Musculoskeletal pain subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Muscle spasms subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Pain in Extremity subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 8		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported