Clinical trial results:
A Phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-small cell lung cancer (NSCLC) metastatic to the brain and/or to leptomeninges

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2014-000578-20
Trial protocol	ES FR GB DE NL BE IT
Global end of trial date	06 February 2019

Results information

Result version number	v1 (current)
This version publication date	22 February 2020
First version publication date	22 February 2020

Trial information

Trial identification

Sponsor protocol code	CLDK378A2205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02336451
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on Investigator assessment per Response evaluation criteria in solid tumors (*RECIST 1.1)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2015
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	Belgium: 2
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Singapore: 2

Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	156
EEA total number of subjects	86

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)	129
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 156 patients were enrolled and treated with ceritinib. The FAS (N=156) included all patients who received at least one dose of ceritinib with 42, 40, 12, 44 and 18 patients in arms 1 to 5 respectively. The Safety set was identical to full analysis set in this study.

Pre-assignment

Screening details:

Approximately 160 patients were planned to be enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1 (PrALKi=Y, PrBRad=Y)

Arm description:

Participants with metastases in the brain without evidence of leptomeningeal carcinomatosis (LC), previously treated with radiation to the brain and with prior exposure to an Anaplastic lymphoma kinase inhibitor (ALK-I). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Ceritinib (LDK378) was administered orally once daily at a dose of 750 mg (5 x 150 mg capsules) on a continuous dosing schedule in fasted conditions. No reference therapy was administered in this study.

Arm title	Arm 2 (PrALKi=Y, PrBRad=N)

Arm description:

Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain but with prior exposure to an ALK-I. Previous treatment with ALK-I other than crizotinib was not allowed in this arm 2 as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Ceritinib (LDK378) was administered orally once daily at a dose of 750 mg (5 x 150 mg capsules) on a continuous dosing schedule in fasted conditions. No reference therapy was administered in this study.

Arm title	Arm 3 (PrALKi=N, PrBRad=Y)

Arm description:

Participants with metastases in the brain without evidence of LC, previously treated with radiation to the brain but with no prior exposure to an ALK-I. Participants in this arm had to present with active brain

lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Ceritinib (LDK378) was administered orally once daily at a dose of 750 mg (5 x 150 mg capsules) on a continuous dosing schedule in fasted conditions. No reference therapy was administered in this study.

Arm title	Arm 4 (PrALKi=N, PrBRad=N)

Arm description:

Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain and with no prior exposure to an ALK-I. Participants in this arm had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Ceritinib (LDK378) was administered orally once daily at a dose of 750 mg (5 x 150 mg capsules) on a continuous dosing schedule in fasted conditions. No reference therapy was administered in this study.

Arm title	Arm 5 (LepDis)

Arm description:

Participants had LC with or without evidence of active lesion at the baseline Gadolinium-enhanced brain magnetic resonance imaging (MRI). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3.

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Ceritinib (LDK378) was administered orally once daily at a dose of 750 mg (5 x 150 mg capsules) on a continuous dosing schedule in fasted conditions. No reference therapy was administered in this study.

Number of subjects in period 1	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)
Started	42	40	12
Completed	0	0	0
Not completed	42	40	12
Adverse event, serious fatal	6	2	3
Physician decision	9	6	7
Adverse event, non-fatal	1	2	-
Patient/guardian decision	2	4	-

Progressive disease	23	26	2
Protocol deviation	1	-	-

Number of subjects in period 1	Arm 4 (PrALKi=N, PrBRad=N)	Arm 5 (LepDis)
Started	44	18
Completed	0	0
Not completed	44	18
Adverse event, serious fatal	6	6
Physician decision	16	3
Adverse event, non-fatal	6	4
Patient/guardian decision	2	1
Progressive disease	14	4
Protocol deviation	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1 (PrALKi=Y, PrBRad=Y)
Reporting group description:	
Participants with metastases in the brain without evidence of leptomeningeal carcinomatosis (LC), previously treated with radiation to the brain and with prior exposure to an Anaplastic lymphoma kinase inhibitor (ALK-I). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).	
Reporting group title	Arm 2 (PrALKi=Y, PrBRad=N)
Reporting group description:	
Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain but with prior exposure to an ALK-I. Previous treatment with ALK-I other than crizotinib was not allowed in this arm 2 as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).	
Reporting group title	Arm 3 (PrALKi=N, PrBRad=Y)
Reporting group description:	
Participants with metastases in the brain without evidence of LC, previously treated with radiation to the brain but with no prior exposure to an ALK-I. Participants in this arm had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).	
Reporting group title	Arm 4 (PrALKi=N, PrBRad=N)
Reporting group description:	
Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain and with no prior exposure to an ALK-I. Participants in this arm had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).	
Reporting group title	Arm 5 (LepDis)
Reporting group description:	
Participants had LC with or without evidence of active lesion at the baseline Gadolinium-enhanced brain magnetic resonance imaging (MRI). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3.	

Reporting group values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)
Number of subjects	42	40	12
Age categorical Units: Subjects			
Adults (18-64 years)	38	31	10
From 65-84 years	4	9	2
Age Continuous Units: years			
arithmetic mean	48.6	54.5	50.0
standard deviation	± 11.37	± 12.32	± 9.67
Sex: Female, Male Units:			
Female	21	19	6
Male	21	21	6
Race/Ethnicity, Customized Units: Subjects			
Asian	18	11	7
Black	0	0	0
Caucasian	24	27	4

Other	0	2	1
Unknown	0	0	0

Reporting group values	Arm 4 (PrALKi=N, PrBRad=N)	Arm 5 (LepDis)	Total
Number of subjects	44	18	156
Age categorical Units: Subjects			
Adults (18-64 years)	36	14	129
From 65-84 years	8	4	27
Age Continuous Units: years			
arithmetic mean	51.8	49.9	
standard deviation	± 11.21	± 11.38	-
Sex: Female, Male Units:			
Female	27	9	82
Male	17	9	74
Race/Ethnicity, Customized Units: Subjects			
Asian	8	3	47
Black	1	0	1
Caucasian	32	15	102
Other	2	0	5
Unknown	1	0	1

Subject analysis sets

Subject analysis set title	Ceritinib 750mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants all received a dose of 750 mg orally in fasted state

Reporting group values	Ceritinib 750mg		
Number of subjects	145		
Age categorical Units: Subjects			
Adults (18-64 years)	129		
From 65-84 years	27		
Age Continuous Units: years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male Units:			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Asian			

Black Caucasian Other Unknown			

End points

End points reporting groups

Reporting group title	Arm 1 (PrALKi=Y, PrBRad=Y)

Reporting group description:

Participants with metastases in the brain without evidence of leptomeningeal carcinomatosis (LC), previously treated with radiation to the brain and with prior exposure to an Anaplastic lymphoma kinase inhibitor (ALK-I). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Reporting group title	Arm 2 (PrALKi=Y, PrBRad=N)

Reporting group description:

Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain but with prior exposure to an ALK-I. Previous treatment with ALK-I other than crizotinib was not allowed in this arm 2 as of protocol amendment 3 and had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Reporting group title	Arm 3 (PrALKi=N, PrBRad=Y)

Reporting group description:

Participants with metastases in the brain without evidence of LC, previously treated with radiation to the brain but with no prior exposure to an ALK-I. Participants in this arm had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Reporting group title	Arm 4 (PrALKi=N, PrBRad=N)

Reporting group description:

Participants with metastases in the brain without evidence of LC, previously untreated with radiation to the brain and with no prior exposure to an ALK-I. Participants in this arm had to present with active brain lesion defined as a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation).

Reporting group title	Arm 5 (LepDis)

Reporting group description:

Participants had LC with or without evidence of active lesion at the baseline Gadolinium-enhanced brain magnetic resonance imaging (MRI). Previous treatment with ALK-I other than crizotinib was not allowed in this arm as of protocol amendment 3.

Subject analysis set title	Ceritinib 750mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants all received a dose of 750 mg orally in fasted state

Primary: Overall response rate (ORR) per Investigator assessment

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

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best overall confirmed response of complete response (CR) or partial response (PR) in the whole
body as assessed per RECIST 1.1 by the investigator. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a nontarget
lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least
30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Primary

End point timeframe:

43 months

Notes:

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

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	35.7 (21.6 to 52.0)	30.0 (16.6 to 46.5)	50.0 (21.1 to 78.9)	59.1 (43.2 to 73.7)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	16.7 (3.6 to 41.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Investigator assessment

End point title	Disease Control Rate (DCR) per Investigator assessment

End point description:

DCR: percentage of parts. with best overall response of CR, PR or stable disease (SD) in the whole body, as assessed per RECIST 1.1 by investigator. CR: Disappearance of all nonnodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed and non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	66.7 (50.5 to 80.4)	82.5 (67.2 to 92.7)	66.7 (34.9 to 90.1)	70.5 (54.8 to 83.2)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	66.7 (41.0 to 86.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Intracranial Response Rate (OIRR) per modified RECIST 1.1 per Investigator assessment

End point title	Overall Intracranial Response Rate (OIRR) per modified RECIST 1.1 per Investigator assessment

End point description:

OIRR was calculated based on response assessments in the brain for patients having measurable brain metastases at baseline. OIRR was defined as the percentage of participants with a best overall confirmed response of CR or PR in the brain as assessed per modified RECIST 1.1. This was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or decreased by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	29	7	33
Units: Percentage of participants				
number (confidence interval 95%)	39.3 (21.5 to 59.4)	27.6 (12.7 to 47.2)	28.6 (3.7 to 71.0)	51.5 (33.5 to 69.2)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage of participants				
number (confidence interval 95%)	12.5 (0.3 to 52.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Intracranial Response Rate (OIRR) per modified RECIST 1.1 per Blinded Independent Review Committee (BIRC) assessment

End point title	Overall Intracranial Response Rate (OIRR) per modified RECIST 1.1 per Blinded Independent Review Committee (BIRC) assessment

End point description:

OIRR was calculated based on response assessments in the brain for patients having measurable brain metastases at baseline. OIRR was defined as the percentage of participants with a best overall confirmed response of CR or PR in the brain as assessed per modified RECIST 1.1. This was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or decreased by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	29	6	34
Units: Percentage of participants				
number (confidence interval 95%)	33.3 (17.3 to 52.8)	24.1 (10.3 to 43.5)	33.3 (4.3 to 77.7)	58.8 (40.7 to 75.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (confidence interval 95%)	20.0 (2.5 to 55.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per Investigator assessment at Weeks 8 & 16

End point title	Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per Investigator assessment at Weeks 8 & 16

End point description:

IDCR overall: percentage of participants with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1 by the Investigator. This
was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in
size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

Week 8 and Week 16

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)				
IDCR at Week 8	71.4 (55.4 to 84.3)	75.0 (58.8 to 87.3)	58.3 (27.7 to 84.8)	68.2 (52.4 to 81.4)
IDCR at Week 16	59.5 (43.3 to 74.4)	62.5 (45.8 to 77.3)	58.3 (27.7 to 84.8)	65.9 (50.1 to 79.5)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)				
IDCR at Week 8	66.7 (41.0 to 86.7)			
IDCR at Week 16	50.0 (26.0 to 74.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per Investigator assessment - Overall

End point title	Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per Investigator assessment - Overall

End point description:

IDCR overall: percentage of participants with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1 by the Investigator. This
was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in

size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	71.4 (55.4 to 84.3)	85.0 (70.2 to 94.3)	75.0 (42.8 to 94.5)	75.0 (59.7 to 86.8)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	66.7 (41.0 to 86.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per BIRC assessment at Weeks 8 & 16

End point title	Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per BIRC assessment at Weeks 8 & 16

End point description:

IDCR overall: percentage of participants with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1 by Investigator. This was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

Week 8 and Week 16

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)				
IDCR at 8 weeks	76.2 (60.5 to 87.9)	80.0 (64.4 to 90.9)	58.3 (27.7 to 84.8)	68.2 (52.4 to 81.4)
IDCR at 16 weeks	69.0 (52.9 to 82.4)	62.5 (45.8 to 77.3)	58.3 (27.7 to 84.8)	68.2 (52.4 to 81.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)				
IDCR at 8 weeks	66.7 (41.0 to 86.7)			
IDCR at 16 weeks	38.9 (17.3 to 64.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per BIRC assessment - Overall

End point title	Intracranial Disease Control Rate (IDCR) per modified RECIST 1.1 per BIRC assessment - Overall

End point description:

IDCR overall: percentage of participants with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1 by Investigator. This was applied to the brain only. CR: Disappearance of all non-nodal target & non-target lesions. All lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	73.8 (58.0 to 86.1)	85.0 (70.2 to 94.3)	66.7 (34.9 to 90.1)	75.0 (59.7 to 86.8)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	66.7 (41.0 to 86.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to intracranial tumor response (TTIR) per modified RECIST 1.1 per Investigator assessment

End point title	Time to intracranial tumor response (TTIR) per modified RECIST 1.1 per Investigator assessment

End point description:

TTIR was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the brain as assessed per modified RECIST 1.1 criteria for patients with measurable brain metastases at baseline. This was applied to the brain only. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	2	17
Units: months				
median (full range (min-max))	1.87 (1.7 to 7.5)	1.84 (1.6 to 9.1)	3.56 (1.8 to 5.3)	1.77 (1.3 to 7.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: months				
median (full range (min-max))	1.80 (1.8 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to intracranial tumor response (TTIR) per modified RECIST 1.1 per BIRC assessment

End point title	Time to intracranial tumor response (TTIR) per modified RECIST 1.1 per BIRC assessment

End point description:

TTIR was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the brain as assessed per modified RECIST 1.1 criteria for patients with measurable brain metastases at baseline. This was applied to the brain only. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	7	2	20
Units: months				
median (full range (min-max))	1.91 (1.7 to 5.6)	1.68 (1.6 to 7.2)	6.31 (3.5 to 9.1)	1.81 (1.3 to 9.2)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (full range (min-max))	1.22 (0.7 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of intracranial response (DOIR) by modified RECIST 1.1 per Investigator assessment

End point title	Duration of intracranial response (DOIR) by modified RECIST 1.1 per Investigator assessment

End point description:

Defined as the time from the first documented response (PR or CR) in the brain to the date of the first documented disease progression in the brain or death due to any cause,
amongst participants with measurable brain metastases at baseline and a confirmed response (PR or CR) in the brain as per modified RECIST 1.1. This was applied to the brain
only. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10
mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions
(taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	2	17
Units: months				
median (confidence interval 95%)	9.2 (3.7 to 999)	10.1 (3.8 to 17.3)	999 (999 to 999)	7.5 (5.6 to 11.2)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: months				
median (confidence interval 95%)	5.5 (0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of intracranial response (DOIR) by modified RECIST 1.1 per BIRC assessment

End point title	Duration of intracranial response (DOIR) by modified RECIST 1.1 per BIRC assessment

End point description:

Defined as the time from the first documented response (PR or CR) in the brain to the date of the first documented disease progression in the brain or death due to any cause,
amongst participants with measurable brain metastases at baseline and a confirmed response (PR or CR) in the brain as per modified RECIST 1.1. CR: Disappearance of all nonnodal
target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is
identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of
diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	7	2	20
Units: months				
median (confidence interval 95%)	11.0 (3.8 to 999)	4.6 (3.5 to 20.3)	99 (18.4 to 999)	9.2 (5.7 to 11.3)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (confidence interval 95%)	3.4 (2.0 to 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Extracranial Response Rate (OERR) per RECIST 1.1 per Investigator & BIRC assessment

End point title	Overall Extracranial Response Rate (OERR) per RECIST 1.1 per Investigator & BIRC assessment

End point description:

OERR was defined as the percentage of participants with a best overall confirmed response of CR or PR outside of the brain, as assessed per RECIST 1.1. CR: Disappearance of
all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new

lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)				
OERR per Investigator assessment	31.0 (17.6 to 47.1)	42.5 (27.0 to 59.1)	41.7 (15.2 to 72.3)	61.4 (45.5 to 75.6)
OERR per BIRC assessment	26.2 (13.9 to 42.0)	25.0 (12.7 to 41.2)	50.0 (21.1 to 78.9)	61.4 (45.5 to 75.6)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)				
OERR per Investigator assessment	22.2 (6.4 to 47.6)			
OERR per BIRC assessment	16.7 (3.6 to 41.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial Disease Control Rate (EDCR) per RECIST 1.1 per Investigator & BIRC assessment - Overall

End point title	Extracranial Disease Control Rate (EDCR) per RECIST 1.1 per Investigator & BIRC assessment - Overall

End point description:

EDCR overall was defined as the percentage of participants with a best overall response of CR, PR or SD outside of the brain as assessed per RECIST 1.1. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed and non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)				
EDCR per Investigator assessment	69.0 (52.9 to 82.4)	92.5 (79.6 to 98.4)	66.7 (34.9 to 90.1)	72.7 (57.2 to 85.0)
EDCR per BIRC assessment	64.3 (48.0 to 78.4)	80.0 (64.4 to 90.9)	66.7 (34.9 to 90.1)	68.2 (52.4 to 81.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)				
EDCR per Investigator assessment	72.2 (46.5 to 90.3)			
EDCR per BIRC assessment	72.2 (46.5 to 90.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial Disease Control Rate (EDCR) per RECIST 1.1 per Investigator & BIRC assessment at weeks 8 & 16

End point title	Extracranial Disease Control Rate (EDCR) per RECIST 1.1 per Investigator & BIRC assessment at weeks 8 & 16

End point description:

EDCR at weeks 8 & 16: defined as percentage of parts. with CR, PR or SD outside of the brain at Wk 8 & 16 extracranial tumor evaluations respectively, per RECIST 1.1. CR:
Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short
axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference
the baseline sum of diameters) is observed and non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

Week 8 and Week 16

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)				
EDCR per Investigator @ Week 8	69.0 (52.9 to 82.4)	82.5 (67.2 to 92.7)	58.3 (27.7 to 84.8)	63.6 (47.8 to 77.6)
EDCR per Investigator @ Week 16	57.1 (41.0 to 72.3)	82.5 (67.2 to 92.7)	66.7 (34.9 to 90.1)	65.9 (50.1 to 79.5)
EDCR per BIRC @ Week 8	66.7 (50.5 to 80.4)	72.5 (56.1 to 85.4)	58.3 (27.7 to 84.8)	61.4 (45.5 to 75.6)
EDCR per BIRC @ Week 16	54.8 (38.7 to 70.2)	70.0 (53.5 to 83.4)	66.7 (34.9 to 90.1)	68.2 (52.4 to 81.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)				
EDCR per Investigator @ Week 8	72.2 (46.5 to 90.3)			
EDCR per Investigator @ Week 16	50.0 (26.0 to 74.0)			
EDCR per BIRC @ Week 8	72.2 (46.5 to 90.3)			
EDCR per BIRC @ Week 16	44.4 (21.5 to 69.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to extracranial tumor response (TTER) per RECIST 1.1 per Investigator assessment

End point title	Time to extracranial tumor response (TTER) per RECIST 1.1 per Investigator assessment

End point description:

TTER was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) outside of the brain as assessed per RECIST 1.1 criteria. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	17	5	27
Units: months				
median (full range (min-max))	1.87 (1.7 to 18.2)	1.87 (1.6 to 9.3)	1.81 (1.2 to 12.7)	1.77 (1.3 to 5.7)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: months				
median (full range (min-max))	2.73 (1.8 to 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to extracranial tumor response (TTER) per RECIST 1.1 per BIRC assessment

End point title	Time to extracranial tumor response (TTER) per RECIST 1.1 per BIRC assessment

End point description:

TTER was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) outside of the brain as assessed per RECIST 1.1 criteria. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	4	27
Units: months				
median (full range (min-max))	1.81 (1.7 to 12.9)	1.86 (1.6 to 22.9)	2.66 (1.7 to 5.5)	1.77 (1.3 to 22.0)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: months				
median (full range (min-max))	1.81 (1.8 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of extracranial response (DOER) per RECIST 1.1 per Investigator assessment

End point title	Duration of extracranial response (DOER) per RECIST 1.1 per Investigator assessment

End point description:

DOER was defined as the time from the first documented response (PR or CR) outside of the brain to the date of the first documented disease progression outside of the brain or death due to any cause, amongst patients with a confirmed response (PR or CR) outside of the brain per RECIST 1.1. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	17	5	27
Units: months				
median (confidence interval 95%)	18.4 (5.6 to 999)	19.3 (5.7 to 999)	999 (999 to 999)	99 (24.4 to 999)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: months				
median (confidence interval 95%)	4.6 (1.9 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of extracranial response (DOER) per RECIST 1.1 per BIRC assessment

End point title	Duration of extracranial response (DOER) per RECIST 1.1 per BIRC assessment

End point description:

DOER was defined as the time from the first documented response (PR or CR) outside of the brain to the date of the first documented disease progression outside of the brain or death due to any cause, amongst patients with a confirmed response (PR or CR) outside of the brain per RECIST 1.1. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	6	27
Units: months				
median (confidence interval 95%)	999 (5.5 to 999)	6.0 (3.7 to 27.7)	999 (16.5 to 999)	999 (11.5 to 999)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	5.5 (3.8 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) (whole body) per RECIST 1.1 per BIRC assessment

End point title	Overall response rate (ORR) (whole body) per RECIST 1.1 per BIRC assessment

End point description:

Overall response rate ORR is defined as the percentage of participants with a best overall confirmed response of complete response (CR) or partial response (PR) in the whole body as assessed per RECIST 1.1 by BIRC. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	23.8 (12.1 to 39.5)	15.0 (5.7 to 29.8)	33.3 (9.9 to 65.1)	61.4 (45.5 to 75.6)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	11.1 (1.4 to 34.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) (whole body) per RECIST 1.1 per BIRC assessment

End point title	Disease control rate (DCR) (whole body) per RECIST 1.1 per BIRC assessment

End point description:

DCR: defined as percentage of participants with a best overall response of CR, PR or stable disease (SD) in the whole body, per RECIST 1.1 by BIRC. CR: Disappearance of all nonnodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), & no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed and non-target lesions are not in progression or in complete response. SD: Neither sufficient shrinkage in the target lesion to qualify for PR or CR nor an increase in lesions which would qualify for PD & non-target lesions are not in unequivocal progression.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: Percentage of participants				
number (confidence interval 95%)	61.9 (45.6 to 76.4)	80.0 (64.4 to 90.9)	66.7 (34.9 to 90.1)	68.2 (52.4 to 81.4)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	72.2 (46.5 to 90.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) (whole body) per RECIST 1.1 per Investigator assessment

End point title	Time to tumor response (TTR) (whole body) per RECIST 1.1 per Investigator assessment

End point description:

TTR was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the whole body as assessed per RECIST 1.1 criteria per Investigator. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be nonpathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as

reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	6	26
Units: months				
median (full range (min-max))	1.87 (1.7 to 9.3)	2.00 (1.7 to 9.3)	1.82 (1.2 to 30.1)	1.81 (1.3 to 3.7)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (full range (min-max))	1.91 (1.8 to 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) (whole body) per RECIST 1.1 per BIRC assessment

End point title	Time to tumor response (TTR) (whole body) per RECIST 1.1 per BIRC assessment

End point description:

TTR was defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the whole body as assessed by RECIST 1.1 criteria per BIRC assessment. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be nonpathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	4	27
Units: months				
median (full range (min-max))	2.00 (1.7 to 12.9)	1.76 (1.6 to 1.9)	1.82 (1.7 to 26.5)	1.81 (1.3 to 22.0)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (full range (min-max))	1.86 (1.8 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) (whole body) per RECIST 1.1 per Investigator assessment

End point title	Duration of response (DOR) (whole body) per RECIST 1.1 per Investigator assessment

End point description:

DOR was defined as the time from the first documented response (PR or CR) to the date of the first documented disease progression or death due to any cause, amongst patients with a confirmed response (PR or CR) in the whole body per RECIST 1.1 per Investigator. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	6	26
Units: months				
median (confidence interval 95%)	10.8 (4.1 to 999)	12.8 (3.7 to 17.3)	99 (11.7 to 999)	9.2 (7.3 to 23.9)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	5.5 (3.7 to 9.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) (whole body) per RECIST 1.1 per BIRC assessment

End point title	Duration of response (DOR) (whole body) per RECIST 1.1 per BIRC assessment

End point description:

DOR was defined as the time from the first documented response (PR or CR) to the date of the first documented disease progression or death due to any cause, amongst patients with a confirmed response (PR or CR) in the whole body per RECIST 1.1 per BIRC. CR: Disappearance of all non-nodal target and non-target lesions. In addition, all lymph nodes assigned a target or a non-target lesions must be non-pathological in size (< 10 mm short axis), and no new lesion is identified. PR: When all target lesions have disappeared or
there is a decrease by at least 30% in the sum of diameter of all target lesions (taking as reference the baseline sum of diameters) is observed & non-target lesions are not in
progression or in complete response.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	4	27
Units: months				
median (confidence interval 95%)	11.0 (2.0 to 999)	10.6 (3.7 to 20.3)	999 (16.5 to 999)	9.2 (5.7 to 14.3)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (confidence interval 95%)	5.7 (5.5 to 6.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) (whole body) per RECIST 1.1 per Investigator & BIRC assessment

End point title	Progression free survival (PFS) (whole body) per RECIST 1.1 per Investigator & BIRC assessment

End point description:

PFS was defined as the time from the date of the first dose of ceritinib to the date of the first radiologically documented disease progression in the whole body per RECIST 1.1 or death due to any cause. A patient who had not progressed or died at the date of the analysis was censored at the time of the last adequate tumor evaluation on or before the cut-off date.

End point type	Secondary

End point timeframe:

43 months

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: months				
median (confidence interval 95%)				
PFS per Investigator assessment (n=32,35,6,33,14)	7.2 (3.3 to 10.9)	5.6 (3.6 to 9.2)	999 (1.0 to 999)	7.9 (5.5 to 9.4)
PFS per BIRC assessment (n=34,36,8,33,14)	5.0 (3.3 to 9.1)	5.5 (3.6 to 7.3)	15.5 (1.0 to 999)	7.7 (5.5 to 9.7)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)				
PFS per Investigator assessment (n=32,35,6,33,14)	5.2 (1.6 to 7.2)			
PFS per BIRC assessment (n=34,36,8,33,14)	3.6 (1.6 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overal survival (OS)

End point title	Overal survival (OS)

End point description:

OS was defined as time from the date of first dose of ceritinib to the date of death due to any cause. The OS time for patients who were alive at the end of the study or
were lost to follow-up was censored at the date of last contact.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Arm 1 (PrALKi=Y, PrBRad=Y)	Arm 2 (PrALKi=Y, PrBRad=N)	Arm 3 (PrALKi=N, PrBRad=Y)	Arm 4 (PrALKi=N, PrBRad=N)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	12	44
Units: months				
median (confidence interval 95%)	24.0 (12.6 to 999)	999 (16.2 to 999)	999 (1.0 to 999)	999 (26.5 to 999)

End point values	Arm 5 (LepDis)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	7.2 (1.6 to 16.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of ceritinib in study population: Cmax/trough & Cmin/trough

End point title	Pharmacokinetics (PK) of ceritinib in study population: Cmax/trough & Cmin/trough

End point description:

Cmax is the maximum (peak) concentration of drug in plasma.
Cmin is the minimum (trough) concentration of drug in plasma.
Sparse blood samples for ceritinib PK evaluation in plasma were collected on C1D1 up to C6D1 from all patients who received at least one dose of investigational study treatment.

End point type	Secondary

End point timeframe:

Cmax: Cycle 2 Day 1 (C2D1); Cmin: C1D1, C1D8, C1D15, C2D1, C3D1, C4D1, C5D1, C6D1 - all 0hr (pre dose)

End point values	Ceritinib 750mg			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmin C1D1: 0hr. (pre dose) (n=130)	0 (± 0.0)			
Cmin C1D8: 0hr. (pre dose) (n=107)	658 (± 59.2)			
Cmin C1D15: 0hr. (pre dose) (n=106)	846 (± 52.9)			
Cmin C2D1: 0hr. (pre dose) (n=84)	1000 (± 50.0)			
Cmax C2D1: 4 - 10 hrs. (post dose) (n = 73)	1100 (± 47.8)			
Cmin C3D1: 0hr. (pre dose) (n=61)	982 (± 59.1)			
Cmin C4D1: 0hr. (pre dose) (n=46)	978 (± 75.4)			
Cmin C5D1: 0hr. (pre dose) (n=45)	885 (± 75.5)			
Cmin C6D1: 0hr. (pre dose) (n=40)	785 (± 120.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm 1@(PrALKi=Y@PrBRad=Y)
Reporting group description: Arm 1@(PrALKi=Y@PrBRad=Y)	
Reporting group title	Arm 2@(PrALKi=Y@PrBRad=N)
Reporting group description: Arm 2@(PrALKi=Y@PrBRad=N)	
Reporting group title	Arm 3@(PrALKi=N@PrBRad=Y)
Reporting group description: Arm 3@(PrALKi=N@PrBRad=Y)	
Reporting group title	Arm 4@(PrALKi=N@PrBRad=N)
Reporting group description: Arm 4@(PrALKi=N@PrBRad=N)	
Reporting group title	Arm 5@(LepDis)
Reporting group description: Arm 5@(LepDis)	
Reporting group title	All Patients
Reporting group description: All Patients	

Serious adverse events	Arm 1@(PrALKi=Y@PrBRad=Y)	Arm 2@(PrALKi=Y@PrBRad=N)	Arm 3@(PrALKi=N@PrBRad=Y)
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 42 (66.67%)	17 / 40 (42.50%)	4 / 12 (33.33%)
number of deaths (all causes)	8	5	3
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyperthermia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bradyphrenia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory marker increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericardial effusion			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	2 / 42 (4.76%)	2 / 40 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysmetria			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagopleural fistula			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Salivary hypersecretion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Vascular purpura			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Colonic abscess			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection pseudomonal			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nocardia sepsis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 42 (9.52%)	4 / 40 (10.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	1 / 4	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm 4@(PrALKi=N@PrBRad=N)	Arm 5@(LepDis)	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 44 (34.09%)	11 / 18 (61.11%)	75 / 156 (48.08%)
number of deaths (all causes)	6	9	31
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Embolism			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hyperthermia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	3 / 156 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Interstitial lung disease			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			

subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bradyphrenia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Delirium			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hepatic enzyme increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory marker increased			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	4 / 156 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tachycardia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ataxia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysmetria			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	3 / 156 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			

subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 44 (4.55%)	1 / 18 (5.56%)	6 / 156 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Keratitis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagopleural fistula			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary hypersecretion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Vascular purpura			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Colonic abscess			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection pseudomonal			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nocardia sepsis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 44 (2.27%)	2 / 18 (11.11%)	12 / 156 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 2	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences causally related to treatment / all	1 / 3	0 / 1	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm 1@(PrALKi=Y@PrBRad=Y)	Arm 2@(PrALKi=Y@PrBRad=N)	Arm 3@(PrALKi=N@PrBRad=Y)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)	40 / 40 (100.00%)	11 / 12 (91.67%)
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	1 / 12 (8.33%)
occurrences (all)	1	4	1
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 42 (26.19%)	9 / 40 (22.50%)	4 / 12 (33.33%)
occurrences (all)	18	24	6
Fatigue			
subjects affected / exposed	13 / 42 (30.95%)	14 / 40 (35.00%)	3 / 12 (25.00%)
occurrences (all)	19	16	3
Feeling cold			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	4 / 42 (9.52%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
General physical health deterioration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hyperthermia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Influenza like illness			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Malaise			
subjects affected / exposed	0 / 42 (0.00%)	3 / 40 (7.50%)	1 / 12 (8.33%)
occurrences (all)	0	8	1
Non-cardiac chest pain			
subjects affected / exposed	9 / 42 (21.43%)	7 / 40 (17.50%)	1 / 12 (8.33%)
occurrences (all)	11	10	1
Oedema peripheral			

subjects affected / exposed	8 / 42 (19.05%)	6 / 40 (15.00%)	1 / 12 (8.33%)
occurrences (all)	8	7	1
Pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	6 / 42 (14.29%)	14 / 40 (35.00%)	0 / 12 (0.00%)
occurrences (all)	10	19	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 42 (23.81%)	8 / 40 (20.00%)	1 / 12 (8.33%)
occurrences (all)	14	13	1
Dyspnoea			
subjects affected / exposed	4 / 42 (9.52%)	8 / 40 (20.00%)	2 / 12 (16.67%)
occurrences (all)	5	8	2
Dyspnoea exertional			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Haemoptysis			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Productive cough			
subjects affected / exposed	3 / 42 (7.14%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	6	1	1
Psychiatric disorders			

Aggression			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Anxiety			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Bradyphrenia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Disorientation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hallucination, auditory			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hallucinations, mixed			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	3 / 42 (7.14%)	4 / 40 (10.00%)	1 / 12 (8.33%)
occurrences (all)	3	4	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 42 (42.86%)	24 / 40 (60.00%)	3 / 12 (25.00%)
occurrences (all)	31	30	7
Amylase increased			
subjects affected / exposed	2 / 42 (4.76%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Aspartate aminotransferase increased			

subjects affected / exposed	18 / 42 (42.86%)	19 / 40 (47.50%)	2 / 12 (16.67%)
occurrences (all)	36	21	4
Bilirubin conjugated increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 42 (7.14%)	8 / 40 (20.00%)	1 / 12 (8.33%)
occurrences (all)	4	9	1
Blood bilirubin increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 42 (9.52%)	4 / 40 (10.00%)	2 / 12 (16.67%)
occurrences (all)	6	5	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	6 / 42 (14.29%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	10	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 42 (19.05%)	13 / 40 (32.50%)	2 / 12 (16.67%)
occurrences (all)	9	14	2
Lipase increased			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	7	0	0
Neutrophil count decreased			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	6 / 42 (14.29%)	8 / 40 (20.00%)	4 / 12 (33.33%)
occurrences (all)	8	10	4
Weight increased			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Procedural dizziness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Subcutaneous haematoma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Palpitations			
subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Sinus bradycardia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aphasia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Balance disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dizziness			

subjects affected / exposed	6 / 42 (14.29%)	8 / 40 (20.00%)	1 / 12 (8.33%)
occurrences (all)	8	10	1
Dysarthria			
subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Dysgeusia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	12 / 42 (28.57%)	13 / 40 (32.50%)	3 / 12 (25.00%)
occurrences (all)	20	26	8
Memory impairment			
subjects affected / exposed	4 / 42 (9.52%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	5	1	0
Paraesthesia			
subjects affected / exposed	4 / 42 (9.52%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	4	1	0
Partial seizures			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	2 / 42 (4.76%)	4 / 40 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	7	0
Somnolence			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Tremor			
subjects affected / exposed	1 / 42 (2.38%)	3 / 40 (7.50%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 42 (19.05%)	6 / 40 (15.00%)	0 / 12 (0.00%)
occurrences (all)	10	7	0
Neutropenia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1

Thrombocytopenia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 42 (9.52%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	5	0	1
Eye disorders			
Vitreous detachment			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 42 (11.90%)	4 / 40 (10.00%)	1 / 12 (8.33%)
occurrences (all)	5	4	1
Abdominal pain			
subjects affected / exposed	7 / 42 (16.67%)	12 / 40 (30.00%)	4 / 12 (33.33%)
occurrences (all)	11	13	4
Abdominal pain upper			
subjects affected / exposed	6 / 42 (14.29%)	6 / 40 (15.00%)	1 / 12 (8.33%)
occurrences (all)	7	6	1
Bowel movement irregularity			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	10 / 42 (23.81%)	9 / 40 (22.50%)	2 / 12 (16.67%)
occurrences (all)	12	9	3
Diarrhoea			
subjects affected / exposed	27 / 42 (64.29%)	34 / 40 (85.00%)	8 / 12 (66.67%)
occurrences (all)	51	63	15
Dyspepsia			
subjects affected / exposed	7 / 42 (16.67%)	6 / 40 (15.00%)	1 / 12 (8.33%)
occurrences (all)	8	6	1
Dysphagia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	3	1	1
Epigastric discomfort			

subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Faecaloma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ileus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	1
Nausea			
subjects affected / exposed	23 / 42 (54.76%)	29 / 40 (72.50%)	8 / 12 (66.67%)
occurrences (all)	36	42	14
Stomatitis			
subjects affected / exposed	3 / 42 (7.14%)	2 / 40 (5.00%)	0 / 12 (0.00%)
occurrences (all)	5	2	0
Vomiting			
subjects affected / exposed	22 / 42 (52.38%)	24 / 40 (60.00%)	4 / 12 (33.33%)
occurrences (all)	42	48	7
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Dry skin			
subjects affected / exposed	2 / 42 (4.76%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	3 / 42 (7.14%)	3 / 40 (7.50%)	2 / 12 (16.67%)
occurrences (all)	3	3	2

Rash			
subjects affected / exposed	4 / 42 (9.52%)	6 / 40 (15.00%)	4 / 12 (33.33%)
occurrences (all)	6	6	5
Rash maculo-papular			
subjects affected / exposed	3 / 42 (7.14%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Skin fissures			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin striae			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 42 (11.90%)	5 / 40 (12.50%)	2 / 12 (16.67%)
occurrences (all)	6	5	3
Back pain			
subjects affected / exposed	9 / 42 (21.43%)	8 / 40 (20.00%)	1 / 12 (8.33%)
occurrences (all)	9	8	1
Coccydynia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Flank pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle hypertrophy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	3 / 42 (7.14%)	5 / 40 (12.50%)	0 / 12 (0.00%)
occurrences (all)	4	7	0
Muscular weakness			
subjects affected / exposed	4 / 42 (9.52%)	3 / 40 (7.50%)	0 / 12 (0.00%)
occurrences (all)	5	4	0
Musculoskeletal chest pain			
subjects affected / exposed	3 / 42 (7.14%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	6 / 42 (14.29%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	6	1	2
Myalgia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Myopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Pain in extremity			
subjects affected / exposed	2 / 42 (4.76%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	2	1

Infections and infestations			
Influenza			
subjects affected / exposed	1 / 42 (2.38%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	7	1
Mucosal infection			
subjects affected / exposed	2 / 42 (4.76%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Oral candidiasis			
subjects affected / exposed	2 / 42 (4.76%)	3 / 40 (7.50%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Pneumonia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tuberculosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 42 (7.14%)	2 / 40 (5.00%)	2 / 12 (16.67%)
occurrences (all)	3	2	2
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)	4 / 40 (10.00%)	0 / 12 (0.00%)
occurrences (all)	3	6	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 42 (50.00%)	14 / 40 (35.00%)	3 / 12 (25.00%)
occurrences (all)	26	16	4
Hypercalcaemia			

subjects affected / exposed	0 / 42 (0.00%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	4 / 42 (9.52%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	4	3	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 42 (4.76%)	2 / 40 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Hypocalcaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	8 / 42 (19.05%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	12	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 40 (2.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypophagia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 40 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypophosphataemia			
subjects affected / exposed	4 / 42 (9.52%)	1 / 40 (2.50%)	0 / 12 (0.00%)
occurrences (all)	5	2	0

Non-serious adverse events	Arm 4@(PrALKi=N@PrBRad=N)	Arm 5@(LepDis)	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)	18 / 18 (100.00%)	154 / 156 (98.72%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	1	1	8
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	9 / 44 (20.45%)	5 / 18 (27.78%)	38 / 156 (24.36%)
occurrences (all)	12	6	66
Fatigue			
subjects affected / exposed	9 / 44 (20.45%)	3 / 18 (16.67%)	42 / 156 (26.92%)
occurrences (all)	11	3	52
Feeling cold			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	2	2
Gait disturbance			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	6 / 156 (3.85%)
occurrences (all)	1	1	7
General physical health deterioration			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences (all)	1	0	3
Hyperthermia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	3 / 44 (6.82%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	3	0	5
Malaise			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	5 / 156 (3.21%)
occurrences (all)	0	1	10
Non-cardiac chest pain			
subjects affected / exposed	3 / 44 (6.82%)	0 / 18 (0.00%)	20 / 156 (12.82%)
occurrences (all)	5	0	27
Oedema peripheral			
subjects affected / exposed	2 / 44 (4.55%)	2 / 18 (11.11%)	19 / 156 (12.18%)
occurrences (all)	2	2	20
Pain			
subjects affected / exposed	1 / 44 (2.27%)	2 / 18 (11.11%)	4 / 156 (2.56%)
occurrences (all)	1	2	5
Pyrexia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 18 (5.56%)	24 / 156 (15.38%)
occurrences (all)	3	2	34

Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 44 (13.64%)	4 / 18 (22.22%)	29 / 156 (18.59%)
occurrences (all)	8	4	40
Dyspnoea			
subjects affected / exposed	5 / 44 (11.36%)	2 / 18 (11.11%)	21 / 156 (13.46%)
occurrences (all)	6	2	23
Dyspnoea exertional			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	4 / 156 (2.56%)
occurrences (all)	1	0	4
Haemoptysis			
subjects affected / exposed	3 / 44 (6.82%)	0 / 18 (0.00%)	6 / 156 (3.85%)
occurrences (all)	3	0	6
Oropharyngeal pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	4 / 156 (2.56%)
occurrences (all)	1	1	4
Pleural effusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	1	0	5
Productive cough			
subjects affected / exposed	4 / 44 (9.09%)	1 / 18 (5.56%)	10 / 156 (6.41%)
occurrences (all)	4	1	13
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Agitation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	4 / 156 (2.56%)
occurrences (all)	0	1	4
Anxiety			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	4 / 156 (2.56%)
occurrences (all)	1	0	4

Bradyphrenia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences (all)	0	0	3
Disorientation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Hallucination, auditory			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Hallucinations, mixed			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	4 / 44 (9.09%)	1 / 18 (5.56%)	13 / 156 (8.33%)
occurrences (all)	4	1	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 44 (52.27%)	6 / 18 (33.33%)	74 / 156 (47.44%)
occurrences (all)	33	8	109
Amylase increased			
subjects affected / exposed	3 / 44 (6.82%)	1 / 18 (5.56%)	9 / 156 (5.77%)
occurrences (all)	3	1	9
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 44 (29.55%)	4 / 18 (22.22%)	56 / 156 (35.90%)
occurrences (all)	15	9	85
Bilirubin conjugated increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	3	3
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 44 (13.64%)	2 / 18 (11.11%)	20 / 156 (12.82%)
occurrences (all)	6	2	22
Blood bilirubin increased			

subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	10 / 44 (22.73%)	2 / 18 (11.11%)	22 / 156 (14.10%)
occurrences (all)	21	2	36
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Cardiac murmur			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	8 / 156 (5.13%)
occurrences (all)	0	1	12
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 44 (20.45%)	3 / 18 (16.67%)	35 / 156 (22.44%)
occurrences (all)	14	3	42
Lipase increased			
subjects affected / exposed	8 / 44 (18.18%)	2 / 18 (11.11%)	13 / 156 (8.33%)
occurrences (all)	10	2	19
Neutrophil count decreased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences (all)	1	0	2
Weight decreased			
subjects affected / exposed	2 / 44 (4.55%)	3 / 18 (16.67%)	23 / 156 (14.74%)
occurrences (all)	2	4	28
Weight increased			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	4 / 156 (2.56%)
occurrences (all)	1	1	4
Injury, poisoning and procedural complications			

Procedural dizziness			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Subcutaneous haematoma			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	3
Palpitations			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	4 / 156 (2.56%)
occurrences (all)	0	0	4
Sinus bradycardia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	4 / 156 (2.56%)
occurrences (all)	0	0	4
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 18 (11.11%)	2 / 156 (1.28%)
occurrences (all)	0	2	2
Aphasia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	1	1	2
Balance disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	2 / 156 (1.28%)
occurrences (all)	1	0	2
Dizziness			
subjects affected / exposed	4 / 44 (9.09%)	3 / 18 (16.67%)	22 / 156 (14.10%)
occurrences (all)	4	3	26
Dysarthria			
subjects affected / exposed	1 / 44 (2.27%)	3 / 18 (16.67%)	9 / 156 (5.77%)
occurrences (all)	1	4	10
Dysgeusia			
subjects affected / exposed	5 / 44 (11.36%)	1 / 18 (5.56%)	6 / 156 (3.85%)
occurrences (all)	5	1	6
Headache			

subjects affected / exposed	10 / 44 (22.73%)	4 / 18 (22.22%)	42 / 156 (26.92%)
occurrences (all)	10	5	69
Memory impairment			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	1	1	8
Paraesthesia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 18 (5.56%)	9 / 156 (5.77%)
occurrences (all)	3	1	9
Partial seizures			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	2	2
Seizure			
subjects affected / exposed	2 / 44 (4.55%)	3 / 18 (16.67%)	11 / 156 (7.05%)
occurrences (all)	2	3	14
Somnolence			
subjects affected / exposed	1 / 44 (2.27%)	2 / 18 (11.11%)	5 / 156 (3.21%)
occurrences (all)	1	2	7
Tremor			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	1	0	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 44 (11.36%)	3 / 18 (16.67%)	22 / 156 (14.10%)
occurrences (all)	6	4	27
Neutropenia			
subjects affected / exposed	2 / 44 (4.55%)	2 / 18 (11.11%)	7 / 156 (4.49%)
occurrences (all)	2	2	7
Thrombocytopenia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 44 (4.55%)	0 / 18 (0.00%)	7 / 156 (4.49%)
occurrences (all)	3	0	9
Eye disorders			

Vitreous detachment			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	11 / 156 (7.05%)
occurrences (all)	2	0	12
Abdominal pain			
subjects affected / exposed	6 / 44 (13.64%)	4 / 18 (22.22%)	33 / 156 (21.15%)
occurrences (all)	6	4	38
Abdominal pain upper			
subjects affected / exposed	10 / 44 (22.73%)	2 / 18 (11.11%)	25 / 156 (16.03%)
occurrences (all)	11	2	27
Bowel movement irregularity			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	7 / 44 (15.91%)	4 / 18 (22.22%)	32 / 156 (20.51%)
occurrences (all)	8	4	36
Diarrhoea			
subjects affected / exposed	32 / 44 (72.73%)	6 / 18 (33.33%)	107 / 156 (68.59%)
occurrences (all)	43	6	178
Dyspepsia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 18 (0.00%)	16 / 156 (10.26%)
occurrences (all)	2	0	17
Dysphagia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	0	0	5
Epigastric discomfort			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	3 / 156 (1.92%)
occurrences (all)	0	1	3
Faecaloma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	2	2
Ileus			

subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	1	0	6
Nausea			
subjects affected / exposed	19 / 44 (43.18%)	8 / 18 (44.44%)	87 / 156 (55.77%)
occurrences (all)	28	15	135
Stomatitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	6 / 156 (3.85%)
occurrences (all)	1	0	8
Vomiting			
subjects affected / exposed	13 / 44 (29.55%)	9 / 18 (50.00%)	72 / 156 (46.15%)
occurrences (all)	23	17	137
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences (all)	0	0	3
Dry skin			
subjects affected / exposed	4 / 44 (9.09%)	0 / 18 (0.00%)	6 / 156 (3.85%)
occurrences (all)	4	0	6
Eczema			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Hyperhidrosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	9 / 156 (5.77%)
occurrences (all)	1	0	9
Rash			
subjects affected / exposed	7 / 44 (15.91%)	1 / 18 (5.56%)	22 / 156 (14.10%)
occurrences (all)	8	1	26
Rash maculo-papular			
subjects affected / exposed	2 / 44 (4.55%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	2	0	5

Skin fissures			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Skin striae			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Urinary incontinence			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 18 (0.00%)	15 / 156 (9.62%)
occurrences (all)	4	0	18
Back pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	19 / 156 (12.18%)
occurrences (all)	1	0	19
Coccydynia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Flank pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Joint swelling			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	2	2

Muscle hypertrophy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	4 / 44 (9.09%)	0 / 18 (0.00%)	12 / 156 (7.69%)
occurrences (all)	5	0	16
Muscular weakness			
subjects affected / exposed	0 / 44 (0.00%)	3 / 18 (16.67%)	10 / 156 (6.41%)
occurrences (all)	0	3	12
Musculoskeletal chest pain			
subjects affected / exposed	2 / 44 (4.55%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	2	1	7
Musculoskeletal discomfort			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 44 (4.55%)	1 / 18 (5.56%)	11 / 156 (7.05%)
occurrences (all)	3	1	13
Myalgia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 18 (0.00%)	5 / 156 (3.21%)
occurrences (all)	3	0	6
Myopathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Neck pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 18 (0.00%)	3 / 156 (1.92%)
occurrences (all)	1	0	4
Pain in extremity			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	1	1	7
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 44 (4.55%)	0 / 18 (0.00%)	6 / 156 (3.85%)
occurrences (all)	2	0	12
Mucosal infection			

subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	4 / 156 (2.56%)
occurrences (all)	0	1	4
Nasopharyngitis			
subjects affected / exposed	3 / 44 (6.82%)	0 / 18 (0.00%)	6 / 156 (3.85%)
occurrences (all)	3	0	6
Oral candidiasis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	1	1	7
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 18 (11.11%)	5 / 156 (3.21%)
occurrences (all)	0	2	5
Respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	2 / 156 (1.28%)
occurrences (all)	0	1	2
Tuberculosis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 44 (9.09%)	0 / 18 (0.00%)	11 / 156 (7.05%)
occurrences (all)	5	0	12
Urinary tract infection			
subjects affected / exposed	2 / 44 (4.55%)	2 / 18 (11.11%)	11 / 156 (7.05%)
occurrences (all)	2	2	13
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	1 / 156 (0.64%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 44 (13.64%)	6 / 18 (33.33%)	50 / 156 (32.05%)
occurrences (all)	6	6	58
Hypercalcaemia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 18 (0.00%)	1 / 156 (0.64%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	5 / 44 (11.36%)	4 / 18 (22.22%)	16 / 156 (10.26%)
occurrences (all)	7	4	19

Hypoalbuminaemia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 18 (5.56%)	8 / 156 (5.13%)
occurrences (all)	2	1	8
Hypocalcaemia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 18 (5.56%)	4 / 156 (2.56%)
occurrences (all)	2	1	4
Hypokalaemia			
subjects affected / exposed	1 / 44 (2.27%)	4 / 18 (22.22%)	14 / 156 (8.97%)
occurrences (all)	1	5	19
Hypomagnesaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	3 / 156 (1.92%)
occurrences (all)	0	1	3
Hypophagia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 18 (5.56%)	3 / 156 (1.92%)
occurrences (all)	0	1	3
Hypophosphataemia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 18 (5.56%)	7 / 156 (4.49%)
occurrences (all)	1	1	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2014	The purpose of this amendment was to revise protocol sections and provide additional clarifications on study procedures related to ALK testing and BIRC review.
08 June 2015	The purpose of this amendment was to revise protocol sections and provide additional clarifications related to safety and practical operationalization of the study, based on feedback from participating countries. The amendment reflected the availability of updated safety information and clarified sections of the protocol where additional guidance was required.
11 November 2015	The purpose of this amendment is to revise protocol language regarding the requirement to confirm ALK rearrangement at the Novartis designated central laboratory before initiating treatment with ceritinib.
22 August 2016	Arms of the study and to allow one early analysis CSR. Also to include analysis of the secondary endpoints of IDCR (intracranial disease control rate) and EDCR.
31 May 2017	The purpose of this amendment was to include potential interim analysis for Arm 5 patients in order to get an early assessment of the benefit and risk of ceritinib in patients with leptomeningeal disease, as well as the preliminary exploratory analysis of CSF concentration in relation to available paired matching plasma PK samples.
16 May 2018	The purpose of this amendment was to update the end of study criteria to allow ongoing patients benefiting from ceritinib to continue treatment with ceritinib by rolling over to a separate rollover study (and/or other options for continued treatment with ceritinib that are considered acceptable at the country level such as access to commercially available drug or managed access program). In addition withdrawal of consent language and abbreviations sections of protocol were also updated.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of clinical trial results.

Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: