



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: | |
| <p>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.</p> | |
| 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

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: | |
| <p>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.</p> | |
| 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: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall 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 (\pm 0.0) | | | |
| Cmin C1D8: 0hr. (pre dose) (n=107) | 658 (\pm 59.2) | | | |
| Cmin C1D15: 0hr. (pre dose) (n=106) | 846 (\pm 52.9) | | | |
| Cmin C2D1: 0hr. (pre dose) (n=84) | 1000 (\pm 50.0) | | | |
| Cmax C2D1: 4 - 10 hrs. (post dose) (n = 73) | 1100 (\pm 47.8) | | | |
| Cmin C3D1: 0hr. (pre dose) (n=61) | 982 (\pm 59.1) | | | |
| Cmin C4D1: 0hr. (pre dose) (n=46) | 978 (\pm 75.4) | | | |
| Cmin C5D1: 0hr. (pre dose) (n=45) | 885 (\pm 75.5) | | | |
| Cmin C6D1: 0hr. (pre dose) (n=40) | 785 (\pm 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@PrBR ad=Y) | Arm 2@(PrALKi=Y@PrBR ad=N) | Arm 3@(PrALKi=N@PrBR ad=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@PrBR ad=Y) | Arm 2@ (PrALKi=Y@PrBR ad=N) | Arm 3@ (PrALKi=N@PrBR ad=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 occurrences (all) | 8 / 42 (19.05%) 8 | 6 / 40 (15.00%) 7 | 1 / 12 (8.33%) 1 |
| Pain subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 10 | 14 / 40 (35.00%) 19 | 0 / 12 (0.00%) 0 |
| Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 10 / 42 (23.81%) 14 | 8 / 40 (20.00%) 13 | 1 / 12 (8.33%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 5 | 8 / 40 (20.00%) 8 | 2 / 12 (16.67%) 2 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 1 / 40 (2.50%) 1 | 1 / 12 (8.33%) 1 |
| Haemoptysis subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Pleural effusion subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 40 (7.50%) 3 | 0 / 12 (0.00%) 0 |
| Productive cough subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 6 | 1 / 40 (2.50%) 1 | 1 / 12 (8.33%) 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 occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 8 | 8 / 40 (20.00%) 10 | 4 / 12 (33.33%) 4 |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 2 / 40 (5.00%) 2 | 0 / 12 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural dizziness subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Subcutaneous haematoma subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 1 / 40 (2.50%) 2 | 0 / 12 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 40 (7.50%) 3 | 0 / 12 (0.00%) 0 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 1 / 40 (2.50%) 1 | 0 / 12 (0.00%) 0 |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Aphasia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 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 occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 4 / 42 (9.52%) 5 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Eye disorders Vitreous detachment subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 5 | 4 / 40 (10.00%) 4 | 1 / 12 (8.33%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 11 | 12 / 40 (30.00%) 13 | 4 / 12 (33.33%) 4 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 7 | 6 / 40 (15.00%) 6 | 1 / 12 (8.33%) 1 |
| Bowel movement irregularity subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 10 / 42 (23.81%) 12 | 9 / 40 (22.50%) 9 | 2 / 12 (16.67%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 27 / 42 (64.29%) 51 | 34 / 40 (85.00%) 63 | 8 / 12 (66.67%) 15 |
| Dyspepsia subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 8 | 6 / 40 (15.00%) 6 | 1 / 12 (8.33%) 1 |
| Dysphagia subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | 1 / 40 (2.50%) 1 | 1 / 12 (8.33%) 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 occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 1 / 156 (0.64%) 1 |
| Subcutaneous haematoma subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 1 / 156 (0.64%) 1 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 2 / 156 (1.28%) 3 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 4 / 156 (2.56%) 4 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 4 / 156 (2.56%) 4 |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 18 (11.11%) 2 | 2 / 156 (1.28%) 2 |
| Aphasia subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 18 (5.56%) 1 | 2 / 156 (1.28%) 2 |
| Balance disorder subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 18 (0.00%) 0 | 2 / 156 (1.28%) 2 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 3 / 18 (16.67%) 3 | 22 / 156 (14.10%) 26 |
| Dysarthria subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 3 / 18 (16.67%) 4 | 9 / 156 (5.77%) 10 |
| Dysgeusia subjects affected / exposed occurrences (all) | 5 / 44 (11.36%) 5 | 1 / 18 (5.56%) 1 | 6 / 156 (3.85%) 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 occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 1 / 156 (0.64%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 2 | 0 / 18 (0.00%) 0 | 11 / 156 (7.05%) 12 |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 44 (13.64%) 6 | 4 / 18 (22.22%) 4 | 33 / 156 (21.15%) 38 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 10 / 44 (22.73%) 11 | 2 / 18 (11.11%) 2 | 25 / 156 (16.03%) 27 |
| Bowel movement irregularity subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 156 (0.64%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 7 / 44 (15.91%) 8 | 4 / 18 (22.22%) 4 | 32 / 156 (20.51%) 36 |
| Diarrhoea subjects affected / exposed occurrences (all) | 32 / 44 (72.73%) 43 | 6 / 18 (33.33%) 6 | 107 / 156 (68.59%) 178 |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 0 / 18 (0.00%) 0 | 16 / 156 (10.26%) 17 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 5 / 156 (3.21%) 5 |
| Epigastric discomfort subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 3 / 156 (1.92%) 3 |
| Faecaloma subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 2 | 1 / 156 (0.64%) 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 occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 18 (0.00%) 0 | 1 / 156 (0.64%) 1 |
| Skin striae subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 156 (0.64%) 1 |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 156 (0.64%) 1 |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 156 (0.64%) 1 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 2 / 156 (1.28%) 2 |
| Endocrine disorders Cushingoid subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 1 / 156 (0.64%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 4 | 0 / 18 (0.00%) 0 | 15 / 156 (9.62%) 18 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 18 (0.00%) 0 | 19 / 156 (12.18%) 19 |
| Coccydynia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 2 / 156 (1.28%) 2 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 1 | 2 / 156 (1.28%) 2 |
| Joint swelling subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 18 (5.56%) 2 | 1 / 156 (0.64%) 2 |

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