



Clinical trial results:

A randomized, double-blind, placebo-controlled, multicenter Phase III study of RAD001 adjuvant therapy in high risk patients with Diffuse Large B-Cell Lymphoma (DLBCL) of RAD001 versus matching placebo after patients have achieved complete response with first-line rituximab-chemotherapy

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2008-000498-40 |
| Trial protocol | CZ HU SK AT IT DE GR ES |
| Global end of trial date | 15 June 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 June 2017 |
| First version publication date | 30 June 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001N2301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00790036 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, |

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 | 15 June 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 June 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of everolimus versus matching placebo measured as disease free survival (DFS) in high risk patients with DLBCL after achieving complete response (CR) following first-line R-chemotherapy.

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 | 24 July 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 10 |
| Country: Number of subjects enrolled | Australia: 12 |
| Country: Number of subjects enrolled | Austria: 16 |
| Country: Number of subjects enrolled | Brazil: 15 |
| Country: Number of subjects enrolled | Canada: 48 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | China: 72 |
| Country: Number of subjects enrolled | Colombia: 20 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | Germany: 20 |
| Country: Number of subjects enrolled | Egypt: 16 |
| Country: Number of subjects enrolled | Spain: 41 |
| Country: Number of subjects enrolled | France: 26 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Hong Kong: 3 |
| Country: Number of subjects enrolled | Hungary: 15 |
| Country: Number of subjects enrolled | Israel: 17 |
| Country: Number of subjects enrolled | Italy: 54 |
| Country: Number of subjects enrolled | Japan: 81 |

| | |
|--------------------------------------|--------------------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 31 |
| Country: Number of subjects enrolled | Lebanon: 17 |
| Country: Number of subjects enrolled | Mexico: 2 |
| Country: Number of subjects enrolled | Norway: 2 |
| Country: Number of subjects enrolled | New Zealand: 6 |
| Country: Number of subjects enrolled | Peru: 1 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Russian Federation: 25 |
| Country: Number of subjects enrolled | Saudi Arabia: 4 |
| Country: Number of subjects enrolled | Singapore: 14 |
| Country: Number of subjects enrolled | Slovakia: 3 |
| Country: Number of subjects enrolled | Thailand: 16 |
| Country: Number of subjects enrolled | Turkey: 18 |
| Country: Number of subjects enrolled | United States: 86 |
| Country: Number of subjects enrolled | Venezuela, Bolivarian Republic of: 1 |
| Worldwide total number of subjects | 742 |
| EEA total number of subjects | 224 |

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) | 393 |
| From 65 to 84 years | 347 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Considering a recruitment period of 53 months and a final primary analysis performed after an anticipated duration of 69 months after study start, 727 patients had to be included. Actual enrolled: 742.

Pre-assignment

Screening details:

This was a randomized, double-blind, placebo-controlled, multicenter Phase III study in high risk patients (IPI 3-5) who achieved CR after first-line R-chemotherapy treatment.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | RAD001 (Everolimus) |

Arm description:

RAD001 10 mg (two 5 mg tablets), daily for 12 months

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | RAD001 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Everolimus was formulated as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets. Everolimus was dispensed on Day 1 of each cycle until the end-of-treatment visit.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo was formulated as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets. Matching placebo was dispensed on Day 1 of each cycle until the end-of-treatment visit.

| Number of subjects in period 1 | RAD001 (Everolimus) | Placebo |
|---------------------------------------|--------------------------------|------------------|
| Started | 372 | 370 |
| Untreated participants | 4 ^[1] | 6 ^[2] |
| Completed | 177 | 249 |
| Not completed | 195 | 121 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 18 | 7 |
| Disease progression | 24 | 48 |
| Adverse event, non-fatal | 113 | 44 |
| Administrative problems | 5 | 9 |
| Abnormal lab values | 3 | 2 |
| Lost to follow-up | 1 | 2 |
| Subject/guardian decision | 20 | 7 |
| Protocol deviation | 10 | 2 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These subjects, although randomized, were not treated with study drug due to administrative problems, protocol deviation and subject withdrawal of consent.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These subjects, although randomized, were not treated with study drug due to administrative problems and subject withdrawal of consent.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | RAD001 (Everolimus) |
|-----------------------|---------------------|

Reporting group description:

RAD001 10 mg (two 5 mg tablets), daily for 12 months

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months

| Reporting group values | RAD001 (Everolimus) | Placebo | Total |
|--|------------------------|---------|-------|
| Number of subjects | 372 | 370 | 742 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 192 | 201 | 393 |
| From 65-84 years | 180 | 167 | 347 |
| 85 years and over | 0 | 2 | 2 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 60.6 | 60.9 | |
| standard deviation | ± 13.72 | ± 13.61 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 204 | 166 | 370 |
| Male | 168 | 204 | 372 |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | RAD001 (Everolimus) |
| Reporting group description: | |
| RAD001 10 mg (two 5 mg tablets), daily for 12 months | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Everolimus placebo 10 mg (two 5 mg tablets), daily for 12 months | |

Primary: Disease-free Survival (DFS)

| | |
|--|-----------------------------|
| End point title | Disease-free Survival (DFS) |
| End point description: | |
| DFS was defined as the time from date of randomization to the date of event defined as the first documented relapse of the disease or death due to any cause. Relapse was based on investigator assessment and was assigned only if: It was documented according to Cheson guidelines by an objective radiological assessment method; It was documented by a biopsy proven lymphoma including new or recurrent bone marrow involvement; A new anticancer therapy for lymphoma started with subsequent confirmation of the relapse within 4 weeks of the start of this anticancer therapy | |
| End point type | Primary |
| End point timeframe: | |
| From date of randomization to the date of event defined as the first documented recurrence of the disease, or death due to any cause and up to 6 years | |

| End point values | RAD001 (Everolimus) | Placebo | | |
|-----------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 372 | 370 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 77.8 (72.7 to 82.1) | 77 (72.1 to 81.1) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | DFS statistical analysis |
| Comparison groups | RAD001 (Everolimus) v Placebo |
| Number of subjects included in analysis | 742 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.276 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.22 |

Notes:

[1] - P-value was obtained from the one-sided unstratified log rank test.

Secondary: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from date of randomization to date of death due to any cause. If the patient was not known to have died, survival was censored at the date of the last contact.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization to date of death due to any cause up to around 7 years

| End point values | RAD001 (Everolimus) | Placebo | | |
|-----------------------------------|------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 372 | 370 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 2 years | 90.7 (87 to 93.4) | 88.3 (84.4 to 91.3) | | |
| 3 years | 88 (83.8 to 91.1) | 83.7 (79.3 to 87.3) | | |
| 4 years | 85.4 (80.7 to 89.1) | 80.7 (75.8 to 84.7) | | |
| 5 years | 83.4 (78.1 to 87.5) | 77.4 (71.7 to 82) | | |
| 6 years | 80.3 (71.6 to 86.6) | 77.4 (71.7 to 82) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | OS Statistical analysis |
| Comparison groups | RAD001 (Everolimus) v Placebo |
| Number of subjects included in analysis | 742 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.09 |

Secondary: Lymphoma-specific survival (LSS)

| | |
|-----------------|----------------------------------|
| End point title | Lymphoma-specific survival (LSS) |
|-----------------|----------------------------------|

End point description:

LSS was defined as time from randomization to death as a result of lymphoma.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization to death documented as a result of lymphoma up to 7 years

| End point values | RAD001 (Everolimus) | Placebo | | |
|-----------------------------------|------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 372 | 370 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 2 years | 94.9 (91.8 to 96.8) | 90.5 (86.9 to 93.2) | | |
| 3 years | 93.1 (89.6 to 95.5) | 88.8 (84.9 to 91.8) | | |
| 4 years | 91.6 (87.6 to 94.3) | 86.9 (82.6 to 90.3) | | |
| 5 years | 89.4 (84.6 to 92.8) | 85.4 (80.5 to 89.2) | | |
| 6 years | 89.4 (84.6 to 92.8) | 85.4 (80.5 to 89.2) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | LSS Statistical analysis |
| Comparison groups | RAD001 (Everolimus) v Placebo |
| Number of subjects included in analysis | 742 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 1.07 |

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 reported in this record are from date of 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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

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|-----------------------|------------|
| Reporting group title | Everolimus |
|-----------------------|------------|

Reporting group description:

Everolimus

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All Patients

| Serious adverse events | Everolimus | Placebo | All Patients |
|---|--------------------|-------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 105 / 368 (28.53%) | 62 / 364 (17.03%) | 167 / 732 (22.81%) |
| number of deaths (all causes) | 5 | 2 | 7 |
| number of deaths resulting from adverse events | 2 | 0 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diffuse large B-cell lymphoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 2 / 364 (0.55%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythromelalgia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoedema | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose ulceration | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vein disorder | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| 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 | | | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 368 (0.82%) | 2 / 364 (0.55%) | 5 / 732 (0.68%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| Immune system disorders | | | |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Testicular swelling | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 368 (0.82%) | 2 / 364 (0.55%) | 5 / 732 (0.68%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Granulomatous pneumonitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperventilation | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obliterative bronchiolitis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 368 (1.09%) | 1 / 364 (0.27%) | 5 / 732 (0.68%) |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 368 (0.82%) | 0 / 364 (0.00%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis allergic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device difficult to use | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Biopsy lung | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CD4 lymphocytes decreased | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 368 (0.82%) | 0 / 364 (0.00%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 3 / 364 (0.82%) | 4 / 732 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 2 / 364 (0.55%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital haematoma | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| 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 | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 2 / 364 (0.55%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 368 (1.09%) | 2 / 364 (0.55%) | 6 / 732 (0.82%) |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 3 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 5 / 368 (1.36%) | 1 / 364 (0.27%) | 6 / 732 (0.82%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brachial plexopathy | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central nervous system lesion | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| 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 artery occlusion | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| 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 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| 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 infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| 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 | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalomalacia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Headache | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IVth nerve paresis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 2 / 364 (0.55%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vocal cord paresis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 8 / 368 (2.17%) | 5 / 364 (1.37%) | 13 / 732 (1.78%) |
| occurrences causally related to treatment / all | 8 / 8 | 3 / 5 | 11 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphopenia | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 368 (1.90%) | 4 / 364 (1.10%) | 11 / 732 (1.50%) |
| occurrences causally related to treatment / all | 6 / 7 | 4 / 4 | 10 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 3 / 364 (0.82%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ophthalmoplegia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| 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 | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| 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 | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pityriasis rosea | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash papular | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic epidermal necrolysis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cyst | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Myopathy | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polyarthrititis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus colitis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 2 / 364 (0.55%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 3 / 3 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 1 / 364 (0.27%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Moraxella infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 3 / 368 (0.82%) | 1 / 364 (0.27%) | 4 / 732 (0.55%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 368 (1.90%) | 3 / 364 (0.82%) | 10 / 732 (1.37%) |
| occurrences causally related to treatment / all | 6 / 7 | 2 / 3 | 8 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia cryptococcal | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| 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 klebsiella | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyonephrosis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 0 / 364 (0.00%) | 2 / 732 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 3 / 364 (0.82%) | 4 / 732 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 368 (0.54%) | 1 / 364 (0.27%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 368 (0.00%) | 1 / 364 (0.27%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 368 (0.82%) | 0 / 364 (0.00%) | 3 / 732 (0.41%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 368 (0.27%) | 0 / 364 (0.00%) | 1 / 732 (0.14%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| 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 | Everolimus | Placebo | All Patients |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 348 / 368 (94.57%) | 276 / 364 (75.82%) | 624 / 732 (85.25%) |
| Investigations | | | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 21 / 368 (5.71%) | 5 / 364 (1.37%) | 26 / 732 (3.55%) |
| occurrences (all) | 26 | 7 | 33 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 33 / 368 (8.97%) | 5 / 364 (1.37%) | 38 / 732 (5.19%) |
| occurrences (all) | 41 | 6 | 47 |
| CD4 lymphocytes decreased | | | |
| subjects affected / exposed | 37 / 368 (10.05%) | 18 / 364 (4.95%) | 55 / 732 (7.51%) |
| occurrences (all) | 41 | 21 | 62 |
| Weight decreased | | | |
| subjects affected / exposed | 28 / 368 (7.61%) | 6 / 364 (1.65%) | 34 / 732 (4.64%) |
| occurrences (all) | 30 | 6 | 36 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 19 / 368 (5.16%) | 13 / 364 (3.57%) | 32 / 732 (4.37%) |
| occurrences (all) | 20 | 15 | 35 |
| Nervous system disorders | | | |

| | | | |
|---|--------------------------|-------------------------|---------------------------|
| Dizziness subjects affected / exposed occurrences (all) | 21 / 368 (5.71%) 22 | 27 / 364 (7.42%) 32 | 48 / 732 (6.56%) 54 |
| Dysgeusia subjects affected / exposed occurrences (all) | 25 / 368 (6.79%) 28 | 7 / 364 (1.92%) 7 | 32 / 732 (4.37%) 35 |
| Headache subjects affected / exposed occurrences (all) | 42 / 368 (11.41%) 50 | 31 / 364 (8.52%) 34 | 73 / 732 (9.97%) 84 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 61 / 368 (16.58%) 70 | 18 / 364 (4.95%) 23 | 79 / 732 (10.79%) 93 |
| Leukopenia subjects affected / exposed occurrences (all) | 29 / 368 (7.88%) 50 | 23 / 364 (6.32%) 27 | 52 / 732 (7.10%) 77 |
| Lymphopenia subjects affected / exposed occurrences (all) | 22 / 368 (5.98%) 31 | 13 / 364 (3.57%) 13 | 35 / 732 (4.78%) 44 |
| Neutropenia subjects affected / exposed occurrences (all) | 89 / 368 (24.18%) 146 | 57 / 364 (15.66%) 76 | 146 / 732 (19.95%) 222 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 55 / 368 (14.95%) 81 | 9 / 364 (2.47%) 11 | 64 / 732 (8.74%) 92 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 37 / 368 (10.05%) 45 | 28 / 364 (7.69%) 33 | 65 / 732 (8.88%) 78 |
| Fatigue subjects affected / exposed occurrences (all) | 66 / 368 (17.93%) 81 | 55 / 364 (15.11%) 76 | 121 / 732 (16.53%) 157 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 69 / 368 (18.75%) 94 | 25 / 364 (6.87%) 26 | 94 / 732 (12.84%) 120 |
| Pyrexia | | | |

| | | | |
|--|-------------------------|------------------------|--------------------------|
| subjects affected / exposed occurrences (all) | 62 / 368 (16.85%) 73 | 32 / 364 (8.79%) 38 | 94 / 732 (12.84%) 111 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 25 / 368 (6.79%) | 21 / 364 (5.77%) | 46 / 732 (6.28%) |
| occurrences (all) | 31 | 25 | 56 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 21 / 368 (5.71%) | 4 / 364 (1.10%) | 25 / 732 (3.42%) |
| occurrences (all) | 32 | 5 | 37 |
| Constipation | | | |
| subjects affected / exposed | 19 / 368 (5.16%) | 25 / 364 (6.87%) | 44 / 732 (6.01%) |
| occurrences (all) | 24 | 34 | 58 |
| Diarrhoea | | | |
| subjects affected / exposed | 99 / 368 (26.90%) | 49 / 364 (13.46%) | 148 / 732 (20.22%) |
| occurrences (all) | 143 | 66 | 209 |
| Dry mouth | | | |
| subjects affected / exposed | 23 / 368 (6.25%) | 5 / 364 (1.37%) | 28 / 732 (3.83%) |
| occurrences (all) | 23 | 5 | 28 |
| Mouth ulceration | | | |
| subjects affected / exposed | 57 / 368 (15.49%) | 13 / 364 (3.57%) | 70 / 732 (9.56%) |
| occurrences (all) | 104 | 24 | 128 |
| Nausea | | | |
| subjects affected / exposed | 51 / 368 (13.86%) | 37 / 364 (10.16%) | 88 / 732 (12.02%) |
| occurrences (all) | 68 | 41 | 109 |
| Stomatitis | | | |
| subjects affected / exposed | 166 / 368 (45.11%) | 28 / 364 (7.69%) | 194 / 732 (26.50%) |
| occurrences (all) | 263 | 32 | 295 |
| Vomiting | | | |
| subjects affected / exposed | 34 / 368 (9.24%) | 30 / 364 (8.24%) | 64 / 732 (8.74%) |
| occurrences (all) | 44 | 35 | 79 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 65 / 368 (17.66%) | 40 / 364 (10.99%) | 105 / 732 (14.34%) |
| occurrences (all) | 78 | 49 | 127 |
| Dyspnoea | | | |

| | | | |
|---|-------------------------|------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 32 / 368 (8.70%) 38 | 11 / 364 (3.02%) 11 | 43 / 732 (5.87%) 49 |
| Epistaxis subjects affected / exposed occurrences (all) | 34 / 368 (9.24%) 37 | 2 / 364 (0.55%) 2 | 36 / 732 (4.92%) 39 |
| Pneumonitis subjects affected / exposed occurrences (all) | 24 / 368 (6.52%) 24 | 1 / 364 (0.27%) 1 | 25 / 732 (3.42%) 25 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 36 / 368 (9.78%) 40 | 22 / 364 (6.04%) 25 | 58 / 732 (7.92%) 65 |
| Rash subjects affected / exposed occurrences (all) | 70 / 368 (19.02%) 95 | 31 / 364 (8.52%) 35 | 101 / 732 (13.80%) 130 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 25 / 368 (6.79%) 31 | 16 / 364 (4.40%) 18 | 41 / 732 (5.60%) 49 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 30 / 368 (8.15%) 41 | 31 / 364 (8.52%) 35 | 61 / 732 (8.33%) 76 |
| Back pain subjects affected / exposed occurrences (all) | 22 / 368 (5.98%) 26 | 33 / 364 (9.07%) 34 | 55 / 732 (7.51%) 60 |
| Pain in extremity subjects affected / exposed occurrences (all) | 25 / 368 (6.79%) 26 | 28 / 364 (7.69%) 32 | 53 / 732 (7.24%) 58 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 42 / 368 (11.41%) 51 | 32 / 364 (8.79%) 40 | 74 / 732 (10.11%) 91 |
| Pneumonia subjects affected / exposed occurrences (all) | 23 / 368 (6.25%) 23 | 3 / 364 (0.82%) 3 | 26 / 732 (3.55%) 26 |

| | | | |
|------------------------------------|-------------------|------------------|------------------|
| Sinusitis | | | |
| subjects affected / exposed | 21 / 368 (5.71%) | 11 / 364 (3.02%) | 32 / 732 (4.37%) |
| occurrences (all) | 23 | 13 | 36 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 42 / 368 (11.41%) | 27 / 364 (7.42%) | 69 / 732 (9.43%) |
| occurrences (all) | 56 | 32 | 88 |
| Urinary tract infection | | | |
| subjects affected / exposed | 20 / 368 (5.43%) | 18 / 364 (4.95%) | 38 / 732 (5.19%) |
| occurrences (all) | 25 | 29 | 54 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 43 / 368 (11.68%) | 19 / 364 (5.22%) | 62 / 732 (8.47%) |
| occurrences (all) | 48 | 20 | 68 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 42 / 368 (11.41%) | 13 / 364 (3.57%) | 55 / 732 (7.51%) |
| occurrences (all) | 45 | 13 | 58 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 40 / 368 (10.87%) | 26 / 364 (7.14%) | 66 / 732 (9.02%) |
| occurrences (all) | 50 | 33 | 83 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 32 / 368 (8.70%) | 16 / 364 (4.40%) | 48 / 732 (6.56%) |
| occurrences (all) | 48 | 21 | 69 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 04 March 2010 | The changes in this amendment were based on feedback from Investigators and institutional review boards/ethics committees, everolimus project-level updates and guidelines and clarifications and changes on study procedures and inclusion/exclusion criteria: Changes to criteria included: Bone marrow biopsy result prior to study start must be negative, Evidence of current CNS involvement with lymphoma; Changes to study procedures included: Hepatitis testing, pregnancy testing, and CNS involvement with lymphoma screening, end of treatment visit ≤ 7 days after stopping study drug, definition of relapse disease, additional biomarker assessment, study drug dosing and interruption, and concomitant medications. |
| 08 November 2010 | Several inclusion and exclusion criteria had been revised based on the feedback received from Investigators related to standard of care. As a consequence, the study design, the randomization and the analysis of the primary endpoint were revised: the minimum number of prior R-CHOP treatment cycles was reduced from 6 (in original protocol) to 5 cycles; the enrollment of patients who had received prior R-EPOCH treatment was allowed. Additionally, the randomization scheme was modified to stratify patients according to the type of prior rituximab-chemotherapy they received (R-CHOP vs. R-EPOCH). Patients enrolled in the original protocol were assigned to R-CHOP stratum; the analysis of the primary endpoint (disease-free survival) was modified to now use a stratified log-rank test to account for the new randomization scheme instead of an unstratified log-rank test as planned in the original protocol. This amendment also contained changes to ensure consistency across the everolimus clinical development program. |
| 15 December 2011 | The reason for this amendment was slow enrollment rate. Enrollment in this study had not met the expected rate as per the original assumptions, despite implementing practical and feasible approaches to increase the enrollment rate. The feasibility of the study within reasonable timelines was questionable with the current sample size. Therefore, in order not to jeopardize the feasibility of conducting the study within reasonable timelines, the sample size was modified to ensure completion of the study in a timely manner. The power of the study was reduced from 90% to 80%. Therefore the required number of DFS events was reduced from 374 to 279, resulting in sample size reduction 915 to 687 patients. |
| 15 February 2013 | The reason for this amendment was to include revised definition of relapsed disease, update protocol based on Investigator Brochure Edition 11, include Novartis guidance on prevention of pregnancy in clinical trials, and clarify and make changes on study procedures. |
| 02 September 2013 | The reason for this amendment was to increase the sample size, provide additional information on the unblinding and communication of interim OS results, and to include some clarifications related to study procedures. As the study remained blinded at the time of this amendment, this amendment did not affect the integrity of the study. |
| 10 September 2014 | The reason for the protocol amendment was to modify the censoring rule in the primary endpoint analysis for patients starting a new anticancer therapy; modify the follow-up of tumor assessment for patients starting a new anticancer therapy; and modify the definition of imaging modality change. As the study remained blinded at the time of this amendment, this amendment did not affect the integrity of the study. |

| | |
|--------------|---|
| 29 July 2015 | Globally there was one site that did not receive Amendment 7 approval by Last Patient Last Visit on 15-Jun-2016 (approval received 24-Jun-2016). This amendment was done for the following reasons: to remove the second IA and to conduct the final DFS analysis using a pre-defined fixed cut-off date of 31-Dec-2015 and the number of actual DFS events observed by that date, considering the long median study follow-up of 50 months (and at least 24 months follow-up for all patients by end of December 2015). Since there were fewer DFS events for the final DFS analysis, the power for primary endpoint was also amended; to maintain the interim overall survival (OS) analysis at the final DFS analysis (i.e., one IA for OS was removed) and perform the final OS analysis using a pre-defined fixed cutoff date of 31-Dec-2018 (5 years after randomization of the last patient) and the number of actual OS events observed by that date. Based on the number and timing of deaths observed in this study as of 22-Jun-2015 on pooled (i.e., blinded) data, the current projections suggested that it was highly unlikely that the originally targeted 338 OS events will ever be reached. Since there would be fewer death events at final OS analysis, the power for OS was also amended. |
|--------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported