# Clinical trial results:
# A Phase III, multicenter, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis

| | |
|---|---|
| EudraCT number | 2010-020338-25 |
| Trial protocol | LT ES BE FR HU NL CZ GB DE PT AT FI IT GR BG DK PL |
| Global end of trial date | |

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 08 July 2016 |
| First version publication date | 08 July 2016 |

| | |
|---|---|
| Sponsor protocol code | WA25046 |

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01194570 |
| WHO universal trial number (UTN) | - |

Notes:

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

| | |
|---|---|
| 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:

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|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 24 July 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 July 2015 |
| Global end of trial reached? | No |

Notes:

Main objective of the trial:

To evaluate the efficacy and safety of ocrelizumab compared with placebo in subjects with primary progressive multiple sclerosis (PPMS).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 March 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 11 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Norway: 1 |
| Country: Number of subjects enrolled | Poland: 58 |
| Country: Number of subjects enrolled | Portugal: 18 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | Spain: 74 |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Country: Number of subjects enrolled | Austria: 16 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Finland: 12 |
| Country: Number of subjects enrolled | France: 106 |
| Country: Number of subjects enrolled | Germany: 57 |
| Country: Number of subjects enrolled | Greece: 7 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Lithuania: 5 |
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Brazil: 11 |
| Country: Number of subjects enrolled | Canada: 32 |

| | |
|---|---|
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Israel: 17 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Peru: 5 |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | Ukraine: 74 |
| Country: Number of subjects enrolled | United States: 101 |
| Worldwide total number of subjects | 732 |
| EEA total number of subjects | 465 |

Notes:

| | |
|---|---|
| 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) | 732 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Recruitment details: -

Screening details:

A total of 943 subjects were screened and 732 were randomized into the study, of which 725 received at least one dose of placebo or ocrelizumab. A total of 549 subjects were ongoing with double-blind treatment at the clinical cut-off date (CCOD).

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

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| | Placebo |

Arm description:

Subjects with primary progressive multiple sclerosis (PPMS) received placebo matched to ocrelizumab at a schedule interval of 24 weeks up to at least 120 weeks.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received placebo infusions matching ocrelizumab infusions of 300 milligram (mg) separated by 14 days, at a schedule interval of 24 weeks.

| | |
|---|---|
| | Ocrelizumab 600 mg |

Arm description:

Subjects with PPMS received ocrelizumab administered, at a scheduled interval of every 24 weeks up to at least 120 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ocrelizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received ocrelizumab 600 mg intraveous (IV) as 300 mg infusions separated by 14 days, at a scheduled interval of every 24 weeks.

| | Placebo | Ocrelizumab 600 mg |
|---|---|---|
| Started | 244 | 488 |
| Completed | 0 | 0 |
| Not completed | 244 | 488 |
| Physician decision | 2 | 6 |
| Protocol violation | - | 2 |
| Death | 1 | 3 |
| Other | 13 | 20 |
| Pregnancy | 1 | 1 |
| Adverse event | 12 | 18 |
| Non-compliance | 2 | 2 |
| Non-compliance with study drug | 2 | 2 |
| Ongoing at CCOD | 162 | 387 |
| Lost to follow-up | 1 | 4 |
| Lack of efficacy | 27 | 21 |
| Withdrawal by subject | 21 | 22 |

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Subjects with primary progressive multiple sclerosis (PPMS) received placebo matched to ocrelizumab at a schedule interval of 24 weeks up to at least 120 weeks. | |
| Reporting group title | Ocrelizumab 600 mg |
| Reporting group description: | |
| Subjects with PPMS received ocrelizumab administered, at a scheduled interval of every 24 weeks up to at least 120 weeks. | |

| | Placebo | Ocrelizumab 600 mg | Total |
|---|---|---|---|
| Number of subjects | 244 | 488 | 732 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 44.4 | 44.7 | |
| standard deviation | ± 8.3 | ± 7.9 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 124 | 237 | 361 |
| Male | 120 | 251 | 371 |

| | |
|---|---|
| Number of subjects included in analysis | 731 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0321 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.98 |

| | |
|---|---|
| End point title | Time to Onset of Clinical Disability Progression (CDP) Sustained for at Least 24 Weeks During the Double-Blind Treatment Period |

End point description:

The time to onset of CDP was defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit >=24 weeks (>=161 days) after the initial disability progression. Baseline for the time to onset of CDP is the date of randomisation, independent of the first day of dosing. Disability progression is defined as an increase of >= 1.0 point from baseline EDSS score, if the baseline EDSS value is <=5.5 points (inclusive), or an increase of >=0.5 points, if the baseline EDSS is >5.5 points. ITT population included all randomised subjects in the study. Here, 99999 indicates median, -99999 minimum and 99999 maximum of full range as value observed were censored.

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

End point timeframe:

Up to clinical cut-off date (CCOD) 24 July 2015

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 244 | 487[2] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Notes:

[2] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

| | |
|---|---|
| | Time to onset of CDP sustained for 24 weeks |

Statistical analysis description:

Hazard ratios were estimated by stratified Cox regression. Stratified by geographical region (US vs. ROW) and age (<= 45, >45 years).

| | |
|---|---|
| Comparison groups | Placebo v Ocrelizumab 600 mg |

| | |
|---|---|
| Number of subjects included in analysis | 731 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0365 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.98 |

| | |
|---|---|
| End point title | Change From Baseline in Timed 25-Foot Walk (T25-FW) at Week 120 |

End point description:

ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted geometric mean.

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

End point timeframe:

Baseline, Week 120

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[3] | 473[4] | | |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change from Baseline at Week 120 (n= 174, 397) | 55.097 (39.855 to 71.999) | 38.933 (29.222 to 49.374) | | |

Notes:

[3] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[4] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

| | |
|---|---|
| | T25-FW change from baseline at Week 120 |

Statistical analysis description:

Estimates (back-transformed) based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: log(Post-baseline(BL)/BL) = log(BL 25-FTW) + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + log (BL 25-FTW)*Week. Relative reduction was calculated as -Relative change = -(OCR response-Placebo response)/Placebo response*100%. The 95% CI for relative reduction was obtained using the Bootstrap method.

| | |
|---|---|
| Comparison groups | Placebo v Ocrelizumab 600 mg |

| | |
|---|---|
| Number of subjects included in analysis | 712 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0404 [5] |
| Method | Ranked ANCOVA |
| Parameter estimate | Relative Reduction (%) |
| Point estimate | 29.337 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.618 |
| upper limit | 51.456 |

Notes:

[5] - P-value from a ranked ANCOVA on Percent Change from BL adjusting for rank of BL 25-Foot Timed Walk (25-FTW), Geographical Region (US vs ROW) and Age (<=45, > 45 years); missing observations imputed with LOCF.

| | |
|---|---|
| End point title | Change From Baseline in Total Volume of T2 Lesions at Week 120 |

End point description:

ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted geometric mean.

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

End point timeframe:

From Baseline to Week 120

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 234[6] | 464[7] | | |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | | | | |
| % Change from Baseline to Week 120 (n=183, 400) | 7.426 (4.967 to 9.942) | -3.366 (-4.987 to -1.718) | | |

Notes:

[6] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[7] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

| | |
|---|---|
| | Total Volume of T2 Lesions change at Week 120 |

Statistical analysis description:

Estimates (back-transformed) are based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: log(Post-BL/BL) = log(BL T2 lesion volume) + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + log (BL T2 lesion volume)*Week.

| | |
|---|---|
| Comparison groups | Ocrelizumab 600 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 698 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Ranked ANCOVA |
| Parameter estimate | Ratio of Adjusted Geometric Means |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.876 |
| upper limit | 0.924 |

Notes:

[8] - P-value is from ranked ANCOVA on Percent Change from BL adjusting for rank of BL T2 lesion volume, Geographical Region (US vs ROW) and Age (<=45, > 45 years); missing observations imputed with LOCF.

| | |
|---|---|
| End point title | Percent Change in Total Brain Volume From Week 24 to Week 120 |

End point description:

ITT population included all randomised subjects in the study. Here, least square mean is indicating adjusted mean.

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

End point timeframe:

From Week 24 to Week 120

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203[9] | 407[10] | | |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | -1.093 (-1.236 to -0.951) | -0.902 (-1.004 to -0.799) | | |

Notes:

[9] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[10] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

| | |
|---|---|
| | Percent change in total brain volume |

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week. Relative reduction was calculated as – Relative change = - (OCR response-Placebo response)/Placebo response*100%. The 95% CI for relative reduction was obtained using Bootstrap method.

| | |
|---|---|
| Comparison groups | Placebo v Ocrelizumab 600 mg |

| | |
|---|---|
| Number of subjects included in analysis | 610 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0206 |
| Method | MMRM |
| Parameter estimate | Relative Reduction (%) |
| Point estimate | 17.475 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.206 |
| upper limit | 29.251 |

| | |
|---|---|
| End point title | Change in From Baseline Physical Component Summary Score (PCS) SF-36 Health Survey (SF-36) at Week 120 |

End point description:

The SF-36v2 is a 36-item, self- reported, generic measure of quality of life that has been widely used in multiple disease areas. It is composed of 8 health domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (ME). In brief, scoring for each health domain scale involves (a) recoding item response values, (b) summing recoded response values for all items in a given scale to obtain the scale raw score, (c) transforming scale raw score to a 0−100 score. The PCS score is computed by (a) multiplying each health domain z score by a scale-specific physical factor score coefficient, (b) summing the resulting products, (c) converting the product total to T score. ITT population. Here, n= number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted mean.

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

End point timeframe:

From Baseline to Week 120

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 185[11] | 384[12] | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Change at Week 120 (n= 128, 292) | -1.108 (-2.394 to 0.177) | -0.731 (-1.655 to 0.193) | | |

Notes:

[11] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[12] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

| | |
|---|---|
| | SF-36 PCS change from baseline at Week 120 |

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Change = Baseline PCS Score + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline PCS Score*Week.

| | |
|---|---|
| Comparison groups | Placebo v Ocrelizumab 600 mg |
| Number of subjects included in analysis | 569 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6034 |
| Method | MMRM |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | 0.377 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.048 |
| upper limit | 1.802 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.725 |

| | |
|---|---|
| End point title | Number of Subjects With at Least one Adverse Event (AE) |

End point description:

AEs included infusion related reactions (IRRs) and serious multiple sclerosis (MS) relapses, but excluded non-serious MS relapses. The safety population includes all subjects who received at least one dose of study drug.

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

End point timeframe:

From the first infusion up to the study clinical cut-off date 24 July 2015

| | Placebo | Ocrelizumab 600 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239 | 486 | | |
| Units: subjects | 215 | 462 | | |

No statistical analyses for this end point

| Timeframe for reporting adverse events: | |
|---|---|
| From the first infusion up to the study clinical cut-off date 24 July 2015 | |
| Assessment type | Systematic |

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 18.0 |

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Matching placebo to ocrelizumab was administered as two intravenous infusions separated by 14 days at a schedule interval of 24 weeks in subjects with PPMS. | |
| Reporting group title | Ocrelizumab 600 mg |
| Reporting group description: | |
| Ocrelizumab administered as two IV infusions separated by 14 days at a scheduled interval of every 24 weeks in subjects with PPMS. | |

| | Placebo | Ocrelizumab 600 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 53 / 239 (22.18%) | 99 / 486 (20.37%) | |
| number of deaths (all causes) | 1 | 4 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of the cervix | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaplastic large-cell lymphoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign vaginal neoplasm | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondroma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant fibrous histiocytoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rosai-Dorfman syndrome | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug intolerance | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Cervical polyp | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine prolapse | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

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|---|---|---|---|
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 5 / 486 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post lumbar puncture syndrome | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematuria | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative fever | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural intestinal perforation | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 5 / 486 (1.03%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic neuritis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Primary progressive multiple sclerosis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uhthoff's phenomenon | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paralysis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ileus | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus allergic | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 4 / 486 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarthritis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 6 / 486 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 3 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 239 (0.84%) | 5 / 486 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 3 / 239 (1.26%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendictis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 2 / 486 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess of eyelid | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial pyelonephritis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis viral | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impetigo | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected dermal cyst | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastitis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis aseptic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral pericarditis | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 239 (0.00%) | 1 / 486 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 239 (0.42%) | 0 / 486 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| | Placebo | Ocrelizumab 600 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 179 / 239 (74.90%) | 400 / 486 (82.30%) | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 61 / 239 (25.52%) | 191 / 486 (39.30%) | |
| occurrences (all) | 145 | 480 | |
| Contusion | | | |
| subjects affected / exposed | 19 / 239 (7.95%) | 14 / 486 (2.88%) | |
| occurrences (all) | 22 | 19 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 239 (3.77%) | 25 / 486 (5.14%) | |
| occurrences (all) | 9 | 25 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 32 / 239 (13.39%) | 65 / 486 (13.37%) | |
| occurrences (all) | 46 | 97 | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 239 (4.18%) | 25 / 486 (5.14%) | |
| occurrences (all) | 13 | 30 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 23 / 239 (9.62%) | 27 / 486 (5.56%) | |
| occurrences (all) | 31 | 29 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 24 / 486 (4.94%) | |
| occurrences (all) | 14 | 26 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 23 / 486 (4.73%) | |
| occurrences (all) | 14 | 26 | |
| Nausea | | | |
| subjects affected / exposed | 16 / 239 (6.69%) | 19 / 486 (3.91%) | |
| occurrences (all) | 20 | 21 | |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 22 / 486 (4.53%) | |
| occurrences (all) | 15 | 36 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 239 (3.35%) | 29 / 486 (5.97%) | |
| occurrences (all) | 8 | 36 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 30 / 239 (12.55%) | 37 / 486 (7.61%) | |
| occurrences (all) | 33 | 38 | |
| Insomnia | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 27 / 486 (5.56%) | |
| occurrences (all) | 12 | 30 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Back pain | | | |
| subjects affected / exposed | 36 / 239 (15.06%) | 55 / 486 (11.32%) | |
| occurrences (all) | 50 | 65 | |
| Arthralgia | | | |
| subjects affected / exposed | 21 / 239 (8.79%) | 38 / 486 (7.82%) | |
| occurrences (all) | 28 | 43 | |
| Pain in extremity | | | |
| subjects affected / exposed | 25 / 239 (10.46%) | 32 / 486 (6.58%) | |
| occurrences (all) | 34 | 35 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 19 / 486 (3.91%) | |
| occurrences (all) | 12 | 23 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 65 / 239 (27.20%) | 110 / 486 (22.63%) | |
| occurrences (all) | 117 | 184 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 53 / 239 (22.18%) | 96 / 486 (19.75%) | |
| occurrences (all) | 114 | 214 | |
| Influenza | | | |
| subjects affected / exposed | 21 / 239 (8.79%) | 56 / 486 (11.52%) | |
| occurrences (all) | 24 | 69 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 14 / 239 (5.86%) | 53 / 486 (10.91%) | |
| occurrences (all) | 21 | 72 | |
| Bronchitis | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 29 / 486 (5.97%) | |
| occurrences (all) | 18 | 36 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 12 / 239 (5.02%) | 20 / 486 (4.12%) | |
| occurrences (all) | 15 | 22 | |

Were there any global substantial amendments to the protocol? Yes

| | |
|---|---|
| 03 March 2011 | 1. Clarification of the implementation of 2 separate infusions 14 days apart throughout the study. Implementation of the amended re-treatment regimen consisting of two 300 mg ocrelizumab infusions administered 14 days apart at a scheduled interval of every 24 weeks for all treatment doses of Study WA25046.<br>2. Revision of inclusion / exclusion criteria. The main changes included: 1) the inclusion of subjects with higher age (<=55 years) for a broader PPMS study population and 2) modification of the exclusion criteria to reduce the potential risk of infection to study subjects and to improve clarity of screening criteria.<br>3. Clarifications on prior experience with ocrelizumab development programs in lupus, rheumatoid arthritis<br>(RA) and relapsing-remitting multiple sclerosis (RRMS). |
| 15 June 2012 | 1. Dosing preparation and infusion guidance were revised to simplify the preparation of infusion bags and dosing procedures.<br>2. Specific eligibility cut-off values for immunoglobulin M (IgM) and immunoglobulin G (IgG) were modified to reflect the central lab reference ranges.<br>3. Sites were informed of additional, optional sub-studies conducted at select centers in which subjects could be eligible to participate. |
| 06 February 2015 | 1. An update to the Statistical Considerations and Analytical Plan section of the protocol in line with the Statistical Analysis Plan (SAP) for the study.<br>2. Conversion of optional investigator-sponsored Roche-supported sub-studies to Roche supported exploratory substudies as per current policy of the sponsor.<br>3. Revision of the pre-specified mandatory biomarker analysis plan.<br>4. Inclusion of more detail with respect to the open-label extension phase. |

Notes:

Were there any global interruptions to the trial? No

None reported