# Clinical trial results:
# A Randomized, Phase 3, Controlled, Double-Blind, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Rituximab in Combination With Methotrexate (MTX) Compared to MTX Alone, in Methotrexate-Naive Patients With Active Rheumatoid Arthritis

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2005-002395-15 |
| Trial protocol | FI ES DE BE SE CZ IT GB DK |
| Global end of trial date | 22 July 2013 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 15 July 2016 |
| First version publication date | 07 August 2015 |
| Version creation reason | • Correction of full data set<br>Due to EMA system issues, the record results need correction by the MAH. |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | WA17047 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00299104 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 22 July 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of rituximab in the prevention of progression in structural joint damage and to evaluate the safety of rituximab in participants with active rheumatoid arthritis initiating treatment with MTX.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 January 2006 |
| 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 | United States: 181 |
| Country: Number of subjects enrolled | Norway: 3 |
| Country: Number of subjects enrolled | Spain: 32 |
| Country: Number of subjects enrolled | Sweden: 4 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Czech Republic: 21 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | Germany: 42 |
| Country: Number of subjects enrolled | Italy: 20 |
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Brazil: 43 |
| Country: Number of subjects enrolled | Canada: 29 |
| Country: Number of subjects enrolled | China: 36 |
| Country: Number of subjects enrolled | Guatemala: 22 |
| Country: Number of subjects enrolled | India: 35 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 65 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Panama: 10 |
| Country: Number of subjects enrolled | Peru: 34 |
| Country: Number of subjects enrolled | Philippines: 17 |
| Country: Number of subjects enrolled | Poland: 54 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | Korea, Republic of: 18 |
| Worldwide total number of subjects | 748 |
| EEA total number of subjects | 241 |

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) | 668 |
| From 65 to 84 years | 80 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening was from Day -28 to Day 1 which could be extended to accommodate washout of prohibited medications. Participants randomized to the study were 251, 252 and 252 in placebo+methotrexate arm, rituximab(0.5 g x 2) + methotrexate and rituximab(1.0 g x 2) + methotrexate, respectively, out of which 748 received study drug.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo Plus (+) Methotrexate |

Arm description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

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

Dosage and administration details:

Participants received methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received placebo intravenously on Days 1 and 15.

| | |
|---|---|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received either 0.5 mg or 1.0 mg rituximab intravenously on Days 1 and 15.

| | |
|---|---|
| **Arm title** | Rituximab (0.5 g X 2) + Methotrexate |

Arm description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a

dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

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

Dosage and administration details:

Participants received methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8.

| | |
|---|---|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received rituximab intravenously at a dose of 0.5 g on Days 1 and 15. Subsequent rituximab courses were given every 24 weeks for up to 5 years, as indicated.

| | |
|---|---|
| **Arm title** | Rituximab (1.0 g x 2) + Methotrexate |

Arm description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

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

Dosage and administration details:

Participants received 1.0 mg intravenously on Days 1 and 15. Subsequent treatment courses were given every 24 weeks up to 5 years, as indicated.

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

Dosage and administration details:

7.5 mg escalating by 2.5 mg a week ever 1-2 weeks to achieve 15 mg per week by week 4 and 20 mg per week by Week 8.

| Number of subjects in period 1 | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate |
|---|---|---|---|
| Started | 249 | 249 | 250 |
| Safety/ITT: Received Study Drug | 249 | 249 | 250 |
| Completed Week 24 | 227 | 240 | 241 |
| Completed Week 52 | 213 | 227 | 232 |
| Completed Week 104 | 178 | 213 | 216 |
| Completed | 62 | 77 | 80 |
| Not completed | 187 | 172 | 170 |
| Insufficient therapeutic response | 34 | 13 | 8 |
| Consent withdrawn by subject | 14 | 19 | 9 |
| Death | 1 | 1 | 1 |
| Administrative reasons | 104 | 117 | 135 |
| Refused treatment | 9 | 2 | 2 |
| Adverse event | 14 | 9 | 7 |
| Violation of selection criteria | 1 | 2 | - |
| Lost to follow-up | 9 | 8 | 8 |
| Protocol deviation | 1 | 1 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Safety Follow-Up (SFU) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | SFU: Placebo + Methotrexate |

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | SFU: Rituximab (0.5 g x 2) + Methotrexate |

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | SFU: Rituximab (1.0 g x 2) + Methotrexate |

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| | |
|---|---|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 2** | SFU: Placebo + Methotrexate | SFU: Rituximab (0.5 g x 2) + Methotrexate | SFU: Rituximab (1.0 g x 2) + Methotrexate |
|---|---|---|---|
| Started | 62 | 77 | 80 |
| Entered Extended Safety Follow-Up | 129 | 40 | 51 |
| Completed | 129 | 171 | 176 |
| Not completed | 55 | 41 | 37 |
| Consent withdrawn by subject | 16 | 21 | 11 |
| Failure to return | - | 11 | 20 |
| Death | 3 | 2 | 1 |
| Administrative reasons | 27 | 7 | 5 |
| Lost to follow-up | 9 | - | - |
| Joined | 122 | 135 | 133 |
| Completed Week 104 of Treatment Phase | - | 135 | 133 |
| Entered Safety Follow-Up | 122 | - | - |

## Period 3

| | |
|---|---|
| Period 3 title | Extended Safety Follow-Up (ESFU) Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | ESFU: Placebo + Methotrexate |

Arm description:

At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| | |
|---|---|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| **Arm title** | ESFU: Rituximab (0.5 g x 2) + Methotrexate |

Arm description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| Arm type | No intervention |
|---|---|

No investigational medicinal product assigned in this arm

| **Arm title** | ESFU: Rituximab (1.0 g x 2) + Methotrexate |
|---|---|

Arm description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| Arm type | No intervention |
|---|---|

No investigational medicinal product assigned in this arm

| **Number of subjects in period 3[1]** | ESFU: Placebo + Methotrexate | ESFU: Rituximab (0.5 g x 2) + Methotrexate | ESFU: Rituximab (1.0 g x 2) + Methotrexate |
|---|---|---|---|
| Started | 34 | 40 | 51 |
| Completed | 29 | 31 | 39 |
| Not completed | 5 | 9 | 12 |
| Consent withdrawn by subject | 2 | 4 | 8 |
| Administrative reasons | 1 | 2 | 2 |
| Death | - | 1 | - |
| Lost to follow-up | 2 | 2 | 2 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants with CD19+ B-cell counts below baseline level or less than 80 cells/microliter entered the ESFU period.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo Plus (+) Methotrexate |

Reporting group description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

| Reporting group title | Rituximab (0.5 g X 2) + Methotrexate |
|---|---|

Reporting group description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

| Reporting group title | Rituximab (1.0 g x 2) + Methotrexate |
|---|---|

Reporting group description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

| Reporting group values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate |
|---|---|---|---|
| Number of subjects | 249 | 249 | 250 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>48.06<br>± 12.692 | <br><br>47.87<br>± 13.391 | <br><br>47.89<br>± 13.324 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 192 | 203 | 212 |
| Male | 57 | 46 | 38 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 748 | | |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br><br>- | <br><br><br> | <br><br><br> |
| Gender categorical<br>Units: Subjects | | | |
| Female | 607 | | |

| | | | |
|---|---|---|---|
| Male | 141 | | |

## End points

### End points reporting groups

| Reporting group title | Placebo Plus (+) Methotrexate |
|---|---|

Reporting group description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

| Reporting group title | Rituximab (0.5 g X 2) + Methotrexate |
|---|---|

Reporting group description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

| Reporting group title | Rituximab (1.0 g x 2) + Methotrexate |
|---|---|

Reporting group description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

| Reporting group title | SFU: Placebo + Methotrexate |
|---|---|

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| Reporting group title | SFU: Rituximab (0.5 g x 2) + Methotrexate |
|---|---|

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| Reporting group title | SFU: Rituximab (1.0 g x 2) + Methotrexate |
|---|---|

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

| Reporting group title | ESFU: Placebo + Methotrexate |
|---|---|

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| Reporting group title | ESFU: Rituximab (0.5 g x 2) + Methotrexate |
|---|---|

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| Reporting group title | ESFU: Rituximab (1.0 g x 2) + Methotrexate |
|---|---|

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

## Primary: Change From Baseline in Modified Total Sharp Score (mTSS) From Screening at Week 52

| End point title | Change From Baseline in Modified Total Sharp Score (mTSS) From Screening at Week 52 |
|---|---|

End point description:

Rate of progression in structural joint damage (PJD) by change in Total Modified Sharp Score (TMSS) from screening to Week 52 in the modified intent-to-treat (MITT) population. MITT population included all randomized participants who received at least one infusion and had both screening and post-baseline radiographic assessments at the given time-point for analysis. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing. Modified intent-to-treat (MITT) population includes patients with a screening and at least one post-baseline radiographic evaluation, grouped as randomized. Linear interpolation/extrapolation used for missing data.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline and Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 232[1] | 239[2] | 244[3] | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 1.079 (± 4.0934) | 0.646 (± 1.9196) | 0.359 (± 1.0095) | |

Notes:

[1] - MITT population

[2] - MITT population

[3] - MITT population

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Comparing all three treatment groups. The Closure Principle was used to adjust for multiple comparisons.

| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate |
|---|---|
| Number of subjects included in analysis | 715 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0016 |
| Method | Kruskal-wallis |

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus (vs) Placebo + Methotrexate, stratified for region and baseline rheumatoid factor (RF) status. The Closure Principle was used to adjust for multiple comparisons.

| | |
|---|---|
| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1824 |
| Method | Van-Elteren |

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm vs Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons.

| | |
|---|---|
| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (1.0 g x 2) + Methotrexate |
| Number of subjects included in analysis | 476 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0004 |
| Method | Van-Elteren |

## Secondary: Change From Baseline in Modified Sharp Erosion Score at Week 52

| | |
|---|---|
| End point title | Change From Baseline in Modified Sharp Erosion Score at Week 52 |

End point description:

Rate of PJD by change in modified Sharp erosion score from screening to Week 52. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions.

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

End point timeframe:

Baseline and Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 232[4] | 239[5] | 244[6] | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.738 (± 2.048) | 0.453 (± 1.2065) | 0.233 (± 0.6252) | |

Notes:

[4] - MITT population

[5] - MITT population

[6] - MITT population

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Comparing all three treatment groups; The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

| | |
|---|---|
| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate |
| Number of subjects included in analysis | 715 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0004 |
| Method | Kruskal-wallis |

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

| | |
|---|---|
| Comparison groups | Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1194 |
| Method | Van-Elteren |

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

| | |
|---|---|
| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (1.0 g x 2) + Methotrexate |
| Number of subjects included in analysis | 476 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0001 |
| Method | Van-Elteren |

## Secondary: Percentage of Participants Without Radiographic Progression at Week 52

| End point title | Percentage of Participants Without Radiographic Progression at Week 52 |
|---|---|

End point description:

Percentage of participants without radiographic progression at Week 52, defined as change in total modified Sharp Score (TMSS) ≤ 0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a

range of 0 to 168. A score of 0 would indicate no change.

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 232[7] | 239[8] | 244[9] | |
| Units: Percentage | | | | |
| number (not applicable) | 53.4 | 57.7 | 63.5 | |

Notes:

[7] - MITT population

[8] - MITT population

[9] - MITT population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate |
|---|---|
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3803 [10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.13 |

Notes:

[10] - This was a secondary endpoint in a hierarchical testing structure.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate |
| Number of subjects included in analysis | 476 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0309 [11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.1 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.18 |

Notes:

[11] - This was a secondary endpoint in a hierarchical testing structure.

## Secondary: Percentage of Participants Without Radiographic Progression in Total Erosion Score at Week 52

| End point title | Percentage of Participants Without Radiographic Progression in Total Erosion Score at Week 52 |
|---|---|

End point description:

No radiographic progression is defined as a change in the total erosion score at Week 52 of less than or equal to zero.

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

End point timeframe:

Baseline, Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 232[12] | 239[13] | 244[14] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 54.7 | 59 | 66.8 | |

Notes:

[12] - MITT population

[13] - MITT population

[14] - MITT population

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | = 0.3752 [16] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[15] - Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

[16] - This was a secondary endpoint in a hierarchical testing structure.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and Baseline RF status.

| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) |
|---|---|

| | Methotrexate |
|---|---|
| Number of subjects included in analysis | 476 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0081 [17] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[17] - This was a secondary endpoint in a hierarchical testing structure.

## Secondary: Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 52

| End point title | Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 52 |
|---|---|

End point description:

Rate of progression in structural joint damage (PJD) by change in modified joint space narrowing (JSN) from screening to Week 52. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint space narrowing.

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

End point timeframe:

Baseline and Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 232[18] | 239[19] | 244[20] | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.341 (± 2.2408) | 0.193 (± 0.9422) | 0.126 (± 0.6363) | |

Notes:

[18] - MITT population

[19] - MITT population

[20] - MITT population

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Comparing all three treatment groups

| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate |
|---|---|
| Number of subjects included in analysis | 715 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5939 [21] |
| Method | Kruskal-wallis |

Notes:

[21] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

| | Statistical Analysis 2 |
|---|---|

| Statistical analysis title | |
|---|---|

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

| | |
|---|---|
| Comparison groups | Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5478 [22] |
| Method | Van-Elteren |

Notes:

[22] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

| Statistical analysis title | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

| | |
|---|---|
| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate |
| Number of subjects included in analysis | 476 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3096 [23] |
| Method | Van-Elteren |

Notes:

[23] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

## Secondary: Change From Baseline in the Modified Total Sharp Score at Week 24

| | |
|---|---|
| End point title | Change From Baseline in the Modified Total Sharp Score at Week 24 |

End point description:

The modified Total Sharp Score is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing.

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

End point timeframe:

Baseline, Week 24

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 226[24] | 238[25] | 242[26] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.701 (± 2.9116) | 0.508 (± 1.7349) | 0.328 (± 0.9443) | |

Notes:

[24] - MITT population

[25] - MITT population

[26] - MITT population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Total Erosion Score at Week 24

| End point title | Change From Baseline in the Total Erosion Score at Week 24 |
|---|---|

End point description:

Total Erosion Score is determined by evaluation of fourteen sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces. The Total Erosion Score at Week 24 - Total Erosion Score at baseline is calculated.

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

End point timeframe:

Baseline, Week 24

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 226 | 238 | 242 | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.491 (± 1.3789) | 0.404 (± 1.039) | 0.22 (± 0.5802) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 24

| End point title | Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 24 |
|---|---|

End point description:

Joint Space Narrowing is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint space narrowing.

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

End point timeframe:

Baseline, Week 24

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 226[27] | 238[28] | 242[29] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.21 (± 1.7403) | 0.176 (± 0.8949) | 0.108 (± 0.6118) | |

Notes:

[27] - MITT population

[28] - MITT population

[29] - MITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Without Radiographic Progression at Week 24

| End point title | Percentage of Participants Without Radiographic Progression at Week 24 |
|---|---|

End point description:

Percentage of participants without radiographic progression at Week 24 defined as change in total modified Sharp score (TMSS) ≤ 0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

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

End point timeframe:

Baseline, Week 24

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 233 | 239 | 244 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 59.7 | 65.3 | 71.7 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR50 Response at Week 52

| End point title | Percentage of Participants With American College of Rheumatology (ACR) ACR50 Response at Week 52 |
|---|---|

End point description:

To achieve an ACR50 response requires at least a 50% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 50% improvement in three of five additional measurements from:

The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
Intent to treat (ITT) population includes all randomized participants who received at least one infusion. Patients are considered non-responders if data are missing or from the point of withdrawal, rescue use or receipt of non-permitted Disease-modifying anti-rheumatic drugs (DMARDs).

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

End point timeframe:

Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[30] | 249[31] | 250[32] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 41.8 | 59.4 | 64.8 | |

Notes:

[30] - ITT population

[31] - ITT population

[32] - ITT population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate |
|---|---|
| Number of subjects included in analysis | 498 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [33] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[33] - This was a secondary endpoint in a hierarchical testing structure.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate |
|---|---|
| Number of subjects included in analysis | 499 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [34] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[34] - This was a secondary endpoint in a hierarchical testing structure.

## Secondary: Change From Baseline in the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 52

| End point title | Change From Baseline in the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 52 |
|---|---|

End point description:

DAS28-ESR is calculated from the following formula:
(0.56 * TJC) + (0.28 * SJC) + (0.70 * ln ESR) + (0.014 * GH) TJC = tender joint count, based on 28 joints SJC = swollen joint count, based on 28 joints ESR = erythrocyte sedimentation rate in millimeters per hour (mm/h)
GH = patient's global assessment of disease activity A DAS28-ESR score of 5.1 or above is considered to indicate high disease activity. Participants can also be defined as having low disease activity (DAS28-ESR ≤ 3.2) or remission (DAS28-ESR < 2.6).

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

End point timeframe:

Baseline, Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 244[35] | 247[36] | 248[37] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | -2.33 (± 1.691) | -3.35 (± 1.663) | -3.46 (± 1.64) | |

Notes:

[35] - ITT population

[36] - ITT population

[37] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR70 Response at Week 52

| End point title | Percentage of Participants With American College of Rheumatology (ACR) ACR70 Response at Week 52 |
|---|---|

End point description:

To achieve an ACR70 response requires at least a 70% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 70% improvement in three of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.);

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

End point timeframe:

Baseline, Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[38] | 249[39] | 250[40] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 24.9 | 42.2 | 46.8 | |

Notes:

[38] - ITT population

[39] - ITT population

[40] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With DAS28-ESR Remission at Week 52

| End point title | Percentage of Participants With DAS28-ESR Remission at Week 52 |
|---|---|

End point description:

The DAS28-4(ESR) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28-4(ESR) scores range from 0 - 10.
Remission is defined as achieving a DAS28-ESR score of less than 2.6

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

End point timeframe:

Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 247[41] | 248[42] | 249[43] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 12.6 | 25.4 | 30.5 | |

Notes:

[41] - ITT population

[42] - ITT population

[43] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Good Response at Week 52

| End point title | Percentage of Participants With European League Against Rheumatism (EULAR) Good Response at Week 52 |
|---|---|

End point description:

European League Against Rheumatism (EULAR) criteria reflects an improvement in disease activity and an attainment of a lower degree of disease activity. A good response is defined as an improvement in the DAS28-ESR of >1.2 compared with baseline, and attainment of a DAS28-ESR of <3.2.

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[44] | 249[45] | 250[46] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 18.1 | 39 | 41.6 | |

Notes:

[44] - ITT population

[45] - ITT population

[46] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Major Clinical Response at Week 52

| End point title | Percentage of Participants With Major Clinical Response at Week 52 |
|---|---|

End point description:

Major clinical response is defined as a continuous six-month period of success by the ACR70.
ACR70= 70% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 70% improvement in 3 of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain
HAQ-DI (Health Assessment Questionnaire disability index)
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

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

End point timeframe:

Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[47] | 249[48] | 250[49] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 8.4 | 18.1 | 21.2 | |

Notes:

[47] - ITT population

[48] - ITT population

[49] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With DAS28-ESR Low Disease Activity at Week 52

| End point title | Percentage of Participants With DAS28-ESR Low Disease Activity at Week 52 |
|---|---|

End point description:

The DAS28-4(ESR) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28-4(ESR) scores range from 0 - 10.
Low disease activity is defined as achieving a DAS28-ESR score of less than or equal to 3.2

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

End point timeframe:

Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 247[50] | 248[51] | 249[52] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 19.8 | 40.3 | 43 | |

Notes:

[50] - ITT population

[51] - ITT population

[52] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR20 Response at Week 52

| End point title | Percentage of Participants With American College of Rheumatology (ACR) ACR20 Response at Week 52 |
|---|---|

End point description:

To achieve an ACR20 response requires at least a 20% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 20% improvement in three of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[53] | 249[54] | 250[55] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 64.3 | 76.7 | 80 | |

Notes:

[53] - ITT population

[54] - ITT population

[55] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR90 Response at Week 52

| End point title | Percentage of Participants With American College of Rheumatology (ACR) ACR90 Response at Week 52 |
|---|---|

End point description:

To achieve an ACR90 response requires at least a 90% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 90% improvement in three of five additional measurements from:
The physician's global assessment of disease activity patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[56] | 249[57] | 250[58] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 9.2 | 17.3 | 16.4 | |

Notes:

[56] - ITT population

[57] - ITT population

[58] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score From Baseline at Week 52

| End point title | Change in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score From Baseline at Week 52 |
|---|---|

End point description:

FACIT-F is a 13-item questionnaire. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the participant's response to the questions (with the exception of 2 negatively stated), the greater the participant's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the Participant's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the participant's health status.

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 198[59] | 206[60] | 218[61] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 10.154 (± 11.1344) | 11.833 (± 11.5807) | 12.426 (± 12.2535) | |

Notes:

[59] - ITT population

[60] - ITT population

[61] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 52

| End point title | Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 52 |
|---|---|

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a participant completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip,and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0(without any difficulty) to 4 (unable to do).HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. A negative change from baseline indicates improvement.

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

End point timeframe:

Baseline, Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 248[62] | 247[63] | 249[64] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | -0.8 (± 0.7764) | -1.038 (± 0.7625) | -1.023 (± 0.7634) | |

Notes:

[62] - ITT population

[63] - ITT population

[64] - ITT population

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate stratified for region and RF status.

| Comparison groups | Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate |
|---|---|
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [65] |
| Method | ANOVA |

Notes:

[65] - Secondary endpoint in hierarchical testing structure.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate |
|---|---|
| Number of subjects included in analysis | 497 |
| Analysis specification | Pre-specified |
| Analysis type | other[66] |
| P-value | < 0.0001 [67] |
| Method | ANOVA |

Notes:

[66] - Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

[67] - Secondary endpoint in hierarchical testing structure.

## Secondary: Change From Baseline in the SF-36 Physical Health Component Summary Score at Week 52 and Week 104

| End point title | Change From Baseline in the SF-36 Physical Health Component Summary Score at Week 52 and Week 104 |
|---|---|

End point description:

The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
Means are adjusted for baseline value, Rheumatoid Factor status and region.

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

End point timeframe:

Baseline, Week 52, Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 240[68] | 236[69] | 242[70] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (n=239,236,241) | 8.953 (± 9.3986) | 11.022 (± 9.6246) | 12.205 (± 9.4986) | |
| Week 104 (n=240,236,242) | 8.617 (± 9.85) | 11.032 (± 9.9631) | 12.649 (± 10.4331) | |

Notes:

[68] - ITT population

[69] - ITT population

[70] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the SF-36 Mental Health Component Summary Score at Week 52 and Week 104

| End point title | Change From Baseline in the SF-36 Mental Health Component Summary Score at Week 52 and Week 104 |
|---|---|

End point description:

The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
Means are adjusted for baseline value, Rheumatoid Factor status and region.

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

End point timeframe:

Baseline, Week 52, Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 240[71] | 236[72] | 242[73] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (n=239,236,241) | 6.689 (± 13.116) | 7.718 (± 11.8903) | 8.167 (± 12.1709) | |
| Week 104 (n= 240,236,242) | 6.295 (± 13.9813) | 7.617 (± 12.0793) | 9.066 (± 12.5325) | |

Notes:

[71] - ITT population

[72] - ITT population

[73] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Categorical Change in Health Assessment Questionnaire- Disability Index (HAQ-DI) From Baseline at Week 52

| End point title | Percentage of Participants With Categorical Change in Health Assessment Questionnaire- Disability Index (HAQ-DI) From Baseline at Week 52 |
|---|---|

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each domain has at least two component questions. There are four possible responses for each component on a scale of 0 (without difficulty) to 3 (unable to do). Higher scores = greater dysfunction. Improved:HAQ-DI score change ≤-0.22 Unchanged:HAQ-DI score change -0.22 to 0.22 Worsened:HAQ score ≥0.22

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

End point timeframe:

Baseline, Week 52

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 249[74] | 249[75] | 250[76] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Improved | 77.1 | 86.7 | 86.8 | |
| Unchanged | 14.1 | 8.8 | 8 | |
| Worsened | 8.4 | 3.6 | 4.4 | |
| Not Assessable | 0.4 | 0.8 | 0.8 | |

Notes:

[74] - ITT population

[75] - ITT population

[76] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Minimally Clinically Important Difference (MCID) in the SF-36 Physical Health Component Score at Week 52

| End point title | Percentage of Participants With Minimally Clinically Important Difference (MCID) in the SF-36 Physical Health Component Score at Week 52 |
|---|---|

End point description:

MCID is defined as a change from baseline in SF-36 Physical Health Component Score of >5.42.
SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 239[77] | 236[78] | 242[79] | |
| Units: percentage of participants | | | | |
| number (not applicable) | 63.2 | 69.9 | 76.4 | |

Notes:

[77] - ITT population

[78] - ITT population

[79] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Minimally Clinically Important Difference (MCID) in the Short-Form 36 ( SF-36) Mental Health Component Score at Week 52

| End point title | Percentage of Participants With Minimally Clinically Important Difference (MCID) in the Short-Form 36 ( SF-36) Mental Health Component Score at Week 52 |
|---|---|

End point description:

MCID is defined as a change from baseline in SF-36 Mental Health Component Score of >6.33.
SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.

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

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 239[80] | 236[81] | 242[82] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 49 | 50.8 | 57 | |

Notes:

[80] - ITT population

[81] - ITT population

[82] - ITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Modified Total Sharp Score at Week 104

| End point title | Change From Baseline in the Modified Total Sharp Score at Week 104 |
|---|---|

End point description:

The modified Total Sharp Score is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing.

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

End point timeframe:

Baseline, Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 229 | 238 | 243 | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 1.948 (± 5.5782) | 0.761 (± 2.6181) | 0.406 (± 1.4312) | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Week 104: Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline rheumatoid factor (RF) status

| Comparison groups | Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate |
|---|---|
| Number of subjects included in analysis | 467 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [83] |
| Method | Van-Elteren |

Notes:

[83] - This was a secondary endpoint in a hierarchical testing structure.

## Secondary: Change From Baseline in the Total Erosion Score at Week 104

| End point title | Change From Baseline in the Total Erosion Score at Week 104 |
|---|---|

End point description:

Total Erosion Score is determined by evaluation of 14 sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces). The change from the score at baseline to Week 104 is calculated.

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

End point timeframe:

Baseline, Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 229[84] | 238[85] | 243[86] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 1.315 (± 3.2466) | 0.499 (± 1.7221) | 0.227 (± 0.7939) | |

Notes:

[84] - MITT population

[85] - MITT population

[86] - MITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Without Radiographic Progression at Week 104

| End point title | Percentage of Participants Without Radiographic Progression at Week 104 |
|---|---|

End point description:

Percentage of participants without radiographic progression at Week 104, defined as change in total modified Sharp Score (TMSS) ≤0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

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

End point timeframe:

Baseline, Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 233[87] | 239[88] | 244[89] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 37.3 | 49.4 | 56.6 | |

Notes:

[87] - MITT population

[88] - MITT population

[89] - MITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Without Radiographic Progression in the Total Erosion Score at Week 104

| End point title | Percentage of Participants Without Radiographic Progression in the Total Erosion Score at Week 104 |
|---|---|

End point description:

Total Erosion Score is determined by evaluation of fourteen sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces). The score at baseline is compared to the score at Week 104. No progression is defined as a change from score at screening to Week 104 ≤0.

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

End point timeframe:

Week 104

| End point values | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 233[90] | 239[91] | 244[92] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 38.2 | 52.7 | 58.6 | |

Notes:

[90] - MITT population

[91] - MITT population

[92] - MITT population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 104

| End point title | Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 104 |
|---|---|

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a participant completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. A negative change from baseline indicates improvement.

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

End point timeframe:

Baseline, Week 104

| **End point values** | Placebo Plus (+) Methotrexate | Rituximab (0.5 g X 2) + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 248[93] | 247[94] | 248[95] | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | -0.806 (± 0.7968) | -1038 (± 0.8142) | -1.055 (± 0.7901) | |

Notes:

[93] - ITT population

[94] - ITT population

[95] - ITT population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

| Comparison groups | Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate |
|---|---|
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | other[96] |
| P-value | < 0.0001 |
| Method | ANOVA |

Notes:

[96] - Secondary endpoint in hierarchical testing structure.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placeb

| Comparison groups | Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate |
|---|---|
| Number of subjects included in analysis | 496 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [97] |
| Method | ANOVA |

Notes:

[97] - Secondary endpoint in hierarchical testing structure.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline to End of ESFU, a total of 96 weeks after the end of 3 year Treatment Period.

Adverse event reporting additional description:

Safety Population includes all participants who received at least one dose of study drug, grouped as treated. After Week 104 participants in the placebo group were eligible to receive either Rituximab 2 X 0.5 g + MTX or Rituximab 2 X 1.0g + MTX. Adverse events reported for placebo patients after switching to Rituximab are not included below.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo + Methotrexate |

Reporting group description:

Treatment period : Placebo intravenously on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 g or Rituximab 2 X 1.0 g every 24 weeks. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| | |
|---|---|
| Reporting group title | Rituximab (1.0 g x 2) + Methotrexate |

Reporting group description:

Treatment period: Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was ≥2.6. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| | |
|---|---|
| Reporting group title | Rituximab (0.5 g x 2) + Methotrexate |

Reporting group description:

Treatment period: Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was ≥2.6. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

| **Serious adverse events** | Placebo + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | Rituximab (0.5 g x 2) + Methotrexate |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 48 / 249 (19.28%) | 58 / 263 (22.05%) | 54 / 348 (15.52%) |
| number of deaths (all causes) | 4 | 2 | 4 |
| number of deaths resulting from adverse events | | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaplastic large-cell lymphoma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive Ductal Breast Carcinoma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic Neoplasm | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Monoclonal gammopathy | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paget's disease of nipple | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Primary mediastinal large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer stage II | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carcinoma in situ of skin | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Venous insufficiency | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 2 / 263 (0.76%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical failure | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulcer haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystocele | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 2 / 263 (0.76%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Asthma | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal hypertrophy | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status asthmaticus | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 2 / 263 (0.76%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug dependence | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 3 / 249 (1.20%) | 1 / 263 (0.38%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Accident | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional overdose | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 2 / 263 (0.76%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve sclerosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Ear and labyrinth disorders** | | | |
| Meniere's disease | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Inguinal hernia obstructive | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis Ulcerative | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal dysplasia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal hypomotility | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal polyp | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic ulcer | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| Goitre | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 2 / 263 (0.76%) | 3 / 348 (0.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Spinal pain | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 249 (2.41%) | 4 / 263 (1.52%) | 7 / 348 (2.01%) |
| occurrences causally related to treatment / all | 4 / 6 | 2 / 4 | 1 / 7 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 249 (1.61%) | 0 / 263 (0.00%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 3 / 263 (1.14%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 2 / 348 (0.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| 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 | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colonic abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endophthalmitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 263 (0.00%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 0 / 263 (0.00%) | 1 / 348 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 263 (0.38%) | 0 / 348 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Placebo + Methotrexate | Rituximab (1.0 g x 2) + Methotrexate | Rituximab (0.5 g x 2) + Methotrexate |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 193 / 249 (77.51%) | 208 / 263 (79.09%) | 232 / 348 (66.67%) |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 53 / 249 (21.29%) | 67 / 263 (25.48%) | 69 / 348 (19.83%) |
| occurrences (all) | 100 | 121 | 150 |

| | | | |
|---|---|---|---|
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 18 / 249 (7.23%) | 24 / 263 (9.13%) | 22 / 348 (6.32%) |
| occurrences (all) | 20 | 25 | 27 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 18 / 249 (7.23%) | 31 / 263 (11.79%) | 17 / 348 (4.89%) |
| occurrences (all) | 23 | 40 | 19 |
| Dizziness | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 20 / 263 (7.60%) | 12 / 348 (3.45%) |
| occurrences (all) | 15 | 21 | 14 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 25 / 249 (10.04%) | 19 / 263 (7.22%) | 14 / 348 (4.02%) |
| occurrences (all) | 25 | 23 | 15 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 42 / 249 (16.87%) | 46 / 263 (17.49%) | 45 / 348 (12.93%) |
| occurrences (all) | 51 | 60 | 54 |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 249 (6.02%) | 18 / 263 (6.84%) | 24 / 348 (6.90%) |
| occurrences (all) | 23 | 29 | 25 |
| Dyspepsia | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 14 / 263 (5.32%) | 15 / 348 (4.31%) |
| occurrences (all) | 14 | 14 | 16 |
| Gastritis | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 10 / 263 (3.80%) | 11 / 348 (3.16%) |
| occurrences (all) | 13 | 13 | 12 |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 35 / 249 (14.06%) | 38 / 263 (14.45%) | 37 / 348 (10.63%) |
| occurrences (all) | 47 | 51 | 50 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 11 / 249 (4.42%) | 24 / 263 (9.13%) | 19 / 348 (5.46%) |
| occurrences (all) | 13 | 27 | 24 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 42 / 249 (16.87%) | 29 / 263 (11.03%) | 30 / 348 (8.62%) |
| occurrences (all) | 69 | 47 | 45 |
| Back pain | | | |
| subjects affected / exposed | 14 / 249 (5.62%) | 9 / 263 (3.42%) | 19 / 348 (5.46%) |
| occurrences (all) | 16 | 11 | 20 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 44 / 249 (17.67%) | 58 / 263 (22.05%) | 59 / 348 (16.95%) |
| occurrences (all) | 70 | 126 | 103 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 43 / 249 (17.27%) | 52 / 263 (19.77%) | 53 / 348 (15.23%) |
| occurrences (all) | 71 | 76 | 81 |
| Urinary tract infection | | | |
| subjects affected / exposed | 26 / 249 (10.44%) | 43 / 263 (16.35%) | 36 / 348 (10.34%) |
| occurrences (all) | 40 | 76 | 51 |
| Bronchitis | | | |
| subjects affected / exposed | 15 / 249 (6.02%) | 20 / 263 (7.60%) | 32 / 348 (9.20%) |
| occurrences (all) | 23 | 35 | 39 |
| Sinusitis | | | |
| subjects affected / exposed | 11 / 249 (4.42%) | 20 / 263 (7.60%) | 23 / 348 (6.61%) |
| occurrences (all) | 18 | 28 | 30 |
| Pharyngitis | | | |
| subjects affected / exposed | 16 / 249 (6.43%) | 14 / 263 (5.32%) | 14 / 348 (4.02%) |
| occurrences (all) | 22 | 20 | 22 |
| Influenza | | | |
| subjects affected / exposed | 11 / 249 (4.42%) | 16 / 263 (6.08%) | 9 / 348 (2.59%) |
| occurrences (all) | 15 | 19 | 13 |
| Gastroenteritis | | | |
| subjects affected / exposed | 7 / 249 (2.81%) | 16 / 263 (6.08%) | 9 / 348 (2.59%) |
| occurrences (all) | 8 | 17 | 10 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 March 2006 | Safety information was updated and eligibility criteria and other study procedures were clarified. |
| 09 March 2007 | Enrollment criteria was updated in line with protocol to allow patients who are Hepatitis B core antibody (HbcAb) positive / DNA negative to be enrolled; Safety information (infections including reports of progressive multifocal leukoencephalopathy, PML) was updated. Eligibility criteria and other study procedures were clarified. |
| 24 July 2007 | Sample size and safety information were updated. Study procedures were clarified. |
| 06 March 2009 | Placebo switch dose was amended and safety information updated. Extension of study was specified. Safety information (including PML Update) was updated and study procedures were clarified. |
| 26 November 2009 | This Amendment was to implement dosing discontinuation due to progressive multifocal leukoencephalopathy (PML) reports in Rheumatoid Arthritis (RA) patients. All patients exposed to MabThera (Rituximab) went into safety follow up SFU. |
| 06 September 2012 | This amendment was for termination of extended B cell Safety Follow-UP (SFU). |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported