



## Clinical trial results:

### A RANDOMIZED, DOUBLE-BLIND, STUDY COMPARING THE PHARMACOKINETICS AND PHARMACODYNAMICS, AND ASSESSING THE SAFETY OF PF-05280586 AND RITUXIMAB IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS ON A BACKGROUND OF METHOTREXATE WHO HAVE HAD AN INADEQUATE RESPONSE TO ONE OR MORE TNF ANTAGONIST THERAPIES

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

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-002896-40 |
| Trial protocol           | GB ES DE PL    |
| Global end of trial date | 07 May 2014    |

## Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 11 May 2016   |
| First version publication date | 02 August 2015  |
| Version creation reason        | • New data added to full data set reporting periods and duplicate AEs in their data |

## Trial information

### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | B3281001 |
|-----------------------|----------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01526057 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Pfizer Inc.   |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017                |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, |

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                       | 07 May 2014 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 07 May 2014 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the pharmacokinetic (PK) similarity of rituximab-Pfizer, the rituximab product MabThera (licensed for use in the European Union [EU], hereafter referred to as rituximab-EU) and the rituximab product Rituxan (licensed for use in the United States [US], hereafter referred to as rituximab-US) in participants with active rheumatoid arthritis (RA) on a background of methotrexate (MTX) who have had an inadequate response to 1 or more tumour necrosis factor (TNF) antagonist therapies.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. Safety monitoring was performed throughout the study by an independent data monitoring committee (DMC) at approximately 3-month intervals unless safety concerns requiring their attention arose earlier. In addition, early in the study, an internal review committee monitored safety at monthly intervals for approximately the first 10 months of the study.

Background therapy:

Methotrexate (MTX)

Evidence for comparator:

The mechanism of action of rituximab, which results in profound and prolonged B-cell depletion, precludes the conduct of PK studies in healthy volunteer participants. The population studied in this clinical trial included participants with active RA who were receiving background therapy with MTX and had an inadequate response to 1 or more TNF antagonist therapies. Participants might have been exposed to other biologics, with the exception of any B-cell intervention. This study population reflects the approved, labelled indication for MabThera and Rituxan. Therefore, the treatment regimen provided in the rituximab product labelling was used in the study: 1000 mg rituximab-Pfizer, rituximab-EU, or rituximab-US administered as an intravenous (IV) infusion on Days 1 and 15.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 30 March 2012 |
| 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 Kingdom: 3 |
| Country: Number of subjects enrolled | Germany: 1        |
| Country: Number of subjects enrolled | Australia: 2      |
| Country: Number of subjects enrolled | Canada: 6         |
| Country: Number of subjects enrolled | Colombia: 13      |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Swaziland: 8           |
| Country: Number of subjects enrolled | Israel: 2              |
| Country: Number of subjects enrolled | Mexico: 13             |
| Country: Number of subjects enrolled | Russian Federation: 22 |
| Country: Number of subjects enrolled | United States: 150     |
| Worldwide total number of subjects   | 220                    |
| EEA total number of subjects         | 4                      |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 178 |
| From 65 to 84 years                       | 42  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a multinational, randomised, double-blind, controlled trial in participants with active RA on a background of MTX. The study was conducted at 56 centres in 10 countries. There were a total of 220 participants enrolled in this study: 73 in the rituximab-US arm, 74 in the rituximab-EU arm, and 73 in the rituximab-Pfizer arm.

### Pre-assignment

Screening details:

Participants were screened for up to 4 weeks prior to randomisation.

### Period 1

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

Blinding implementation details:

Study blinded to participant, investigator/study staff, sponsor's study team conducting trial. The study pharmacists preparing treatment infusions were unblinded. The Independent Review Committee and DMC reviewed partially blinded results (ie, treatment groups identified as Arms A, B, and C). Blinding broken in emergency situations when knowledge of treatment assignment was required for medical management for individual subject safety. The investigator notified the sponsor before breaking blind.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Rituximab-Pfizer |

Arm description:

Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|  |                                |
|--|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | PF-05280586 (Rituximab-Pfizer) |
| Investigational medicinal product code |                                |
| Other name                             | Rituximab-Pfizer               |
| Pharmaceutical forms                   | Solution for infusion          |
| Routes of administration               | Intravenous use                |

Dosage and administration details:

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Rituximab-EU |
|------------------|--------------|

Arm description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

**Dosage and administration details:**

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Rituximab-US |
|------------------|--------------|

**Arm description:**

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

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

**Dosage and administration details:**

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

| <b>Number of subjects in period 1</b> | Rituximab-Pfizer | Rituximab-EU | Rituximab-US |
|---------------------------------------|------------------|--------------|--------------|
| Started                               | 73               | 74           | 73           |
| Completed                             | 64               | 71           | 67           |
| Not completed                         | 9                | 3            | 6            |
| Adverse event, serious fatal          | 1                | -            | -            |
| Consent withdrawn by subject          | 3                | 2            | 2            |
| Adverse event, non-fatal              | 3                | 1            | 1            |
| Other                                 | 1                | -            | 1            |
| Lost to follow-up                     | 1                | -            | 1            |
| Protocol deviation                    | -                | -            | 1            |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Rituximab-Pfizer |
|-----------------------|------------------|

Reporting group description:

Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Rituximab-EU |
|-----------------------|--------------|

Reporting group description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Rituximab-US |
|-----------------------|--------------|

Reporting group description:

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

| Reporting group values             | Rituximab-Pfizer | Rituximab-EU | Rituximab-US |
|------------------------------------|------------------|--------------|--------------|
| Number of subjects                 | 73               | 74           | 73           |
| Age categorical<br>Units: Subjects |                  |              |              |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 54.9<br>± 11.52 | 54.9<br>± 11.07 | 53.4<br>± 11.87 |
| Gender categorical<br>Units: Subjects                                   |                 |                 |                 |
| Female  | 59              | 57              | 54              |
| Male  | 14              | 17              | 19              |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 220   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender categorical<br>Units: Subjects                                   |     |  |  |
| Female  | 170 |  |  |
| Male  | 50  |  |  |



## End points

### End points reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Rituximab-Pfizer |
| Reporting group description:<br>Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care. |                  |
| Reporting group title   | Rituximab-EU     |
| Reporting group description:<br>Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.   |                  |
| Reporting group title   | Rituximab-US     |
| Reporting group description:<br>Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.  |                  |

### Primary: Maximum Serum Concentration (Cmax) of Rituximab

|   |   |
|---|---|
| End point title   | Maximum Serum Concentration (Cmax) of Rituximab |
| End point description:<br>Cmax is the peak serum concentration of study drug (rituximab) after a dose has been administered. Per protocol (PP) population: all participants who were randomized, received the full doses of the assigned study treatment, and had no major protocol violations that could impact the PK analysis. Exclusions from the PP population were based on a blinded data review by the Medical Monitor and Clinical Pharmacologist. |   |
| End point type  | Primary   |
| End point timeframe:<br>Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion  |   |

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 68               | 67              | 63              |  |
| Units: ug/mL                         |                  |                 |                 |  |
| arithmetic mean (standard deviation) | 453 (± 153)      | 422 (± 111)     | 430 (± 163)     |  |

## Statistical analyses



|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Rituximab-Pfizer, Rituximab-EU          |
| Statistical analysis description:  |   |
| A 90% confidence interval (CI) on the estimated difference between 2 treatment groups was constructed using a 1-way analysis of variance (ANOVA) model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation. |   |
| Comparison groups  | Rituximab-EU v Rituximab-Pfizer         |
| Number of subjects included in analysis  | 135                                     |
| Analysis specification   | Pre-specified                           |
| Analysis type  | non-inferiority <sup>[1]</sup>          |
| Parameter estimate   | Test-to-reference ratio: adjusted means |
| Point estimate   | 105.67                                  |
| Confidence interval  |   |
| level  | 90 %                                    |
| sides  | 2-sided                                 |
| lower limit  | 96.91                                   |
| upper limit  | 115.21                                  |

Notes:

[1] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinite time (AUC 0-inf) are within the 80.00% to 125.00% range. Rituximab-Pfizer is the numerator.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Rituximab-Pfizer, Rituximab-US          |
| Statistical analysis description:   |   |
| A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation. |   |
| Comparison groups   | Rituximab-Pfizer v Rituximab-US         |
| Number of subjects included in analysis   | 131                                     |
| Analysis specification  | Pre-specified                           |
| Analysis type   | non-inferiority <sup>[2]</sup>          |
| Parameter estimate  | Test-to-reference ratio: adjusted means |
| Point estimate  | 106.62                                  |
| Confidence interval   |   |
| level   | 90 %                                    |
| sides   | 2-sided                                 |
| lower limit   | 97.65                                   |
| upper limit   | 116.41                                  |

Notes:

[2] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range. Rituximab-Pfizer is the numerator.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>   | Rituximab-EU, Rituximab-US  |
| Statistical analysis description:   |                             |
| A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation. |                             |
| Comparison groups   | Rituximab-EU v Rituximab-US |

|   |   |
|---|---|
| Number of subjects included in analysis | 130                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[3]</sup>          |
| Method                                  | ANOVA                                   |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 100.9                                   |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 92.38                                   |
| upper limit                             | 110.2                                   |

Notes:

[3] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in C<sub>max</sub> and AUC 0-inf are within the 80.00% to 125.00% range.

Rituximab-EU is the numerator.

### Primary: AUC 0-inf of Rituximab

|                 |                        |
|-----------------|------------------------|
| End point title | AUC 0-inf of Rituximab |
|-----------------|------------------------|

End point description:

The AUC 0-inf refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) extrapolated to infinity. PP Population

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

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

| End point values                     | Rituximab-Pfizer | Rituximab-EU     | Rituximab-US     |  |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  |  |
| Number of subjects analysed          | 68               | 67               | 62               |  |
| Units: ug/mL/hour                    |                  |                  |                  |  |
| arithmetic mean (standard deviation) | 213000 (± 90400) | 200000 (± 74600) | 214000 (± 95300) |  |

### Statistical analyses

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | Rituximab-Pfizer, Rituximab-EU |
|----------------------------|--------------------------------|

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|                   |                                 |
|-------------------|---------------------------------|
| Comparison groups | Rituximab-Pfizer v Rituximab-EU |
|-------------------|---------------------------------|

|   |   |
|---|---|
| Number of subjects included in analysis | 135                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[4]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 104.19                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 92.75                                   |
| upper limit                             | 117.06                                  |

Notes:

[4] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in C<sub>max</sub> and AUC 0-inf are within the 80.00% to 125.00% range.

Rituximab-Pfizer is the numerator.

For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 104.19 (92.83, 116.93).

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Rituximab-Pfizer, Rituximab-US |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-Pfizer v Rituximab-US         |
| Number of subjects included in analysis | 130                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[5]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 100.45                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 89.2                                    |
| upper limit                             | 113.11                                  |

Notes:

[5] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in C<sub>max</sub> and AUC 0-inf are within the 80.00% to 125.00% range.

Rituximab-Pfizer is the numerator.

For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 100.21 (89.12, 112.67).

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Rituximab-EU, Rituximab-US |
|-----------------------------------|----------------------------|

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-EU v Rituximab-US             |
| Number of subjects included in analysis | 129                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[6]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 96.4                                    |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 85.57                                   |
| upper limit                             | 108.6                                   |

Notes:

[6] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to-reference ratios in C<sub>max</sub> and AUC 0-inf are within the 80.00% to 125.00% range.

Rituximab-EU is the numerator.

For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 96.18 (85.51, 108.19).

### Secondary: Rituximab AUC From Time 0 to 2 Weeks (AUC 0-2wk)

|                 |  |
|-----------------|--|
| End point title | Rituximab AUC From Time 0 to 2 Weeks (AUC 0-2wk) |
|-----------------|--|

End point description:

The AUC 0-2wk refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) to 2 weeks after drug administration.  
PP Population

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

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 68               | 67              | 63              |  |
| Units: ug/mL/hour                    |                  |                 |                 |  |
| arithmetic mean (standard deviation) | 52100 (± 18000)  | 49600 (± 14200) | 49200 (± 15900) |  |

### Statistical analyses

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | Rituximab-Pfizer, Rituximab EU |
|----------------------------|--------------------------------|

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-Pfizer v Rituximab-EU         |
| Number of subjects included in analysis | 135                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[7]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 103.74                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 95.1                                    |
| upper limit                             | 113.15                                  |

Notes:

[7] - Rituximab-Pfizer is the numerator.

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | Rituximab-Pfizer, Rituximab-US |
|----------------------------|--------------------------------|

---

**Statistical analysis description:**

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-Pfizer v Rituximab-US         |
| Number of subjects included in analysis | 131                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[8]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 105.56                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 96.64                                   |
| upper limit                             | 115.3                                   |

Notes:

[8] - Rituximab-Pfizer is the numerator.

---

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Rituximab-EU, Rituximab-US |
|-----------------------------------|----------------------------|

**Statistical analysis description:**

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-EU v Rituximab-US             |
| Number of subjects included in analysis | 130                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[9]</sup>          |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 101.76                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 93.13                                   |
| upper limit                             | 111.18                                  |

Notes:

[9] - Rituximab-EU is the numerator.

---

**Secondary: Rituximab AUC From Time 0 to the Time of the Last Quantifiable Concentration (AUC 0-T)**

|                 |  |
|-----------------|--|
| End point title | Rituximab AUC From Time 0 to the Time of the Last Quantifiable Concentration (AUC 0-T) |
|-----------------|--|

**End point description:**

The AUC 0-T refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) to the last measured concentration at time T. PP Population

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

**End point timeframe:**

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

| <b>End point values</b>              | Rituximab-Pfizer      | Rituximab-EU          | Rituximab-US          |  |
|--------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type                   | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed          | 68                    | 67                    | 63                    |  |
| Units: ug/mL/hour                    |                       |                       |                       |  |
| arithmetic mean (standard deviation) | 198000 ( $\pm$ 79600) | 188000 ( $\pm$ 64300) | 196000 ( $\pm$ 78300) |  |

## Statistical analyses

| <b>Statistical analysis title</b>   | Rituximab-Pfizer, Rituximab-EU          |
|---|---|
| Statistical analysis description:   |   |
| A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation. |   |
| Comparison groups   | Rituximab-Pfizer v Rituximab-EU         |
| Number of subjects included in analysis   | 135                                     |
| Analysis specification  | Pre-specified                           |
| Analysis type   | non-inferiority <sup>[10]</sup>         |
| Parameter estimate  | Test-to-reference ratio: adjusted means |
| Point estimate  | 103.36                                  |
| Confidence interval   |   |
| level   | 90 %                                    |
| sides   | 2-sided                                 |
| lower limit   | 92.81                                   |
| upper limit   | 115.12                                  |

Notes:

[10] - Rituximab-Pfizer is the numerator.

For AUC 0-T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 103.26 (92.13, 115.73).

| <b>Statistical analysis title</b>   | Rituximab-Pfizer, Rituximab-US          |
|---|---|
| Statistical analysis description:   |   |
| A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation. |   |
| Comparison groups   | Rituximab-Pfizer v Rituximab-US         |
| Number of subjects included in analysis   | 131                                     |
| Analysis specification  | Pre-specified                           |
| Analysis type   | non-inferiority <sup>[11]</sup>         |
| Parameter estimate  | Test-to-reference ratio: adjusted means |
| Point estimate  | 101.33                                  |
| Confidence interval   |   |
| level   | 90 %                                    |
| sides   | 2-sided                                 |
| lower limit   | 90.82                                   |
| upper limit   | 113.04                                  |

Notes:

[11] - Rituximab-Pfizer is the numerator.

For AUC 0-T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 100.45 (89.46, 112.79).

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Rituximab-US, Rituximab-EU |
|-----------------------------------|----------------------------|

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

|   |   |
|---|---|
| Comparison groups                       | Rituximab-US v Rituximab-EU             |
| Number of subjects included in analysis | 130                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | non-inferiority <sup>[12]</sup>         |
| Parameter estimate                      | Test-to-reference ratio: adjusted means |
| Point estimate                          | 98.03                                   |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 87.83                                   |
| upper limit                             | 109.4                                   |

Notes:

[12] - Rituximab-EU is the numerator.

For AUC0- T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 97.28 (86.60, 109.27).

### **Secondary: Cluster of Differentiation 19 (CD19+) B-cell Count AUC From Time 0 to the Last Measurement at Time T (AUC 0-T,B-cell)**

|                 |   |
|-----------------|---|
| End point title | Cluster of Differentiation 19 (CD19+) B-cell Count AUC From Time 0 to the Last Measurement at Time T (AUC 0-T,B-cell) |
|-----------------|---|

End point description:

The AUC 0-T,B-cell refers to the concentration in serum of B-cells. It represents the total B-cells over time from time 0 (the point of drug administration) to the last measurement taken at time T. Modified intention-to-treat (mITT) population, defined as all participants who were randomised and received at least 1 dose of study treatment.

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

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (end of trial [EOT])

| <b>End point values</b>              | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 68               | 69              | 67              |  |
| Units: cells/day/mL                  |                  |                 |                 |  |
| arithmetic mean (standard deviation) | 13312 (± 13309)  | 14304 (± 13146) | 12496 (± 13500) |  |

### **Statistical analyses**

No statistical analyses for this end point

**Secondary: Minimum Post-Baseline CD19+ B-cell Count**

|   |  |
|---|--|
| End point title   | Minimum Post-Baseline CD19+ B-cell Count |
| End point description:<br>The lowest CD19+ B-cell count measured in a participant's blood post-baseline. mITT population. |  |
| End point type  | Secondary                                |
| End point timeframe:<br>Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)  |  |

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 68               | 69              | 67              |  |
| Units: /uL                           |                  |                 |                 |  |
| arithmetic mean (standard deviation) | 0 (± 0.28)       | 0 (± 0)         | 0 (± 0.18)      |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Minimum Post-Baseline CD19+ B-cell Count**

|   |  |
|---|--|
| End point title   | Time to Minimum Post-Baseline CD19+ B-cell Count |
| End point description:<br>The amount of time in weeks from baseline to the lowest observed CD19+ B-cell count. mITT population. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)  |  |

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 68               | 69              | 67              |  |
| Units: weeks                         |                  |                 |                 |  |
| arithmetic mean (standard deviation) | 1.4 (± 1.41)     | 1.6 (± 1.68)    | 1.5 (± 1.31)    |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of B-cell depletion (τB-cell)**

|                 |  |
|-----------------|--|
| End point title | Duration of B-cell depletion (τB-cell) |
|-----------------|--|



End point description:

The  $\tau$ B-cell is defined as the time interval over which the B-cell count was  $<0.3$  cells/microliter (uL) or the detection limit. mITT population.

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

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                     | Rituximab-Pfizer  | Rituximab-EU      | Rituximab-US      |  |
|--------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed          | 68                | 69                | 67                |  |
| Units: days                          |                   |                   |                   |  |
| arithmetic mean (standard deviation) | 126 ( $\pm$ 41.8) | 123 ( $\pm$ 38.6) | 120 ( $\pm$ 40.6) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with CD19+ B-cell Count Recovery

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with CD19+ B-cell Count Recovery |
|-----------------|---|

End point description:

The percentage of participants with CD19+ B-cell counts which fell to  $<50\%$  of Baseline value during treatment and which recovered to  $\geq 50\%$  of Baseline value at EOT. mITT population.

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

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 68               | 69              | 67              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           | 4.4              | 8.7             | 9               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under the CD19+ B-cell count concentration-time profile (AUC 0-T, B-cell)

|                 |  |
|-----------------|--|
| End point title | Area under the CD19+ B-cell count concentration-time profile (AUC 0-T, B-cell) |
|-----------------|--|

End point description:

The AUC 0-T, B-cell refers to the CD19+ B-cell count over time. It represents the total B-cells over time, from time 0 (the point of drug administration) to the last measured count at time T.

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

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT). mITT population.

| End point values                     | Rituximab-Pfizer     | Rituximab-EU         | Rituximab-US         |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      |  |
| Number of subjects analysed          | 68                   | 69                   | 67                   |  |
| Units: days/cells/uL                 |                      |                      |                      |  |
| arithmetic mean (standard deviation) | 13312.1 (± 13309.15) | 14304.2 (± 13145.72) | 12495.9 (± 13499.97) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Baseline and Change from Baseline in Circulating Immunoglobulin-M (IgM) by Visit

|                 |  |
|-----------------|--|
| End point title | Baseline and Change from Baseline in Circulating Immunoglobulin-M (IgM) by Visit |
|-----------------|--|

End point description:

The level of IgM in serum at Baseline and the change from Baseline at each subsequent visit. mITT population.

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

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                            | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US     |  |
|---|------------------|-----------------|------------------|--|
| Subject group type                          | Reporting group  | Reporting group | Reporting group  |  |
| Number of subjects analysed                 | 73               | 74              | 73               |  |
| Units: g/L                                  |                  |                 |                  |  |
| arithmetic mean (standard deviation)        |                  |                 |                  |  |
| Baseline (n=73,74,73)                       | 1.381 (± 0.7617) | 1.46 (± 0.8076) | 1.394 (± 0.8372) |  |
| Change from Baseline at Week 1 (n=71,69,70) | 0 (± 0.15)       | 0 (± 0.17)      | 0 (± 0.19)       |  |
| Change from Baseline at Week 2 (n=71,72,68) | 0 (± 0.17)       | 0 (± 0.17)      | 0 (± 0.2)        |  |
| Change from Baseline at Week 3 (n=71,74,69) | -0.1 (± 0.18)    | -0.1 (± 0.17)   | 0 (± 0.15)       |  |
| Change from Baseline at Week 4 (n=68,69,68) | -0.1 (± 0.27)    | -0.1 (± 0.2)    | 0 (± 0.33)       |  |
| Change from Baseline at Week 5 (n=72,71,69) | -0.1 (± 0.3)     | -0.1 (± 0.26)   | -0.1 (± 0.23)    |  |

|  |               |               |               |  |
|--|---------------|---------------|---------------|--|
| Change from Baseline at Week 9<br>(n=68,73,70)       | -0.2 (± 0.32) | -0.3 (± 0.27) | -0.2 (± 0.28) |  |
| Change from Baseline at Week 13<br>(n=67,72,67)      | -0.2 (± 0.52) | -0.3 (± 0.3)  | -0.2 (± 0.55) |  |
| Change from Baseline at Week 17<br>(n=67,71,67)      | -0.1 (± 0.92) | -0.3 (± 0.34) | -0.3 (± 0.34) |  |
| Change from Baseline at Week 21<br>(n=60,65,60)      | -0.3 (± 0.42) | -0.4 (± 0.33) | -0.3 (± 0.35) |  |
| Change from Baseline at Week 25 (EOT;<br>n=50,57,55) | -0.4 (± 0.42) | -0.3 (± 0.3)  | -0.3 (± 0.48) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent (%) Change from Baseline in Circulating IgM by Visit

|   |  |
|---|--|
| End point title   | Percent (%) Change from Baseline in Circulating IgM by Visit |
| End point description:<br>The percentage change from Baseline in circulating IgM by visit. mITT population. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline and Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21 and 25 (EOT)                        |  |

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 72               | 74              | 70              |  |
| Units: g/L                           |                  |                 |                 |  |
| arithmetic mean (standard deviation) |                  |                 |                 |  |
| Week 1 (n=71,69,70)                  | 3.3 (± 18.62)    | 1.4 (± 9.57)    | -0.5 (± 9.93)   |  |
| Week 2 (n=71,72,68)                  | 0.1 (± 12.45)    | -0.3 (± 9.42)   | 0.7 (± 14.06)   |  |
| Week 3 (n=71,74,69)                  | -3.4 (± 12.98)   | -4.9 (± 9.95)   | -2.7 (± 9.82)   |  |
| Week 4 (n=68,69,68)                  | -5.5 (± 14.77)   | -5 (± 10.59)    | -2.2 (± 21.89)  |  |
| Week 5 (n=72,71,69)                  | -8.6 (± 16)      | -7.9 (± 15.6)   | -5.6 (± 14.39)  |  |
| Week 9 (n=68,73,70)                  | -14.4 (± 13.68)  | -16.9 (± 13.69) | -14.1 (± 13.73) |  |
| Week 13 (n=67,72,67)                 | -11.5 (± 37.17)  | -22.2 (± 13.92) | -16.2 (± 30.14) |  |
| Week 17 (n=67,71,67)                 | 5.5 (± 226.39)   | -23.7 (± 16.35) | -21.6 (± 14.88) |  |
| Week 21 (n=60,65,60)                 | -21.6 (± 17.72)  | -24.7 (± 21)    | -21.3 (± 15.69) |  |
| Week 25 (EOT; n=50,57,55)            | -24.2 (± 14.63)  | -21 (± 16.95)   | -20.5 (± 21.78) |  |

## Statistical analyses

**Secondary: Percentage of Participants with American College of Rheumatology (ACR) 20% Improvement (ACR20) Response by Visit**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with American College of Rheumatology (ACR) 20% Improvement (ACR20) Response by Visit |
|-----------------|--|

## End point description:

ACR20 response: greater than or equal to ( $\geq$ )20% improvement in tender joint count;  $\geq$ 20% improvement in swollen joint count; and  $\geq$ 20% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and C-Reactive Protein (CRP). Non-responder imputation categorised participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

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

## End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           |                  |                 |                 |  |
| Week 3 (n=73,74,73)               | 34.2             | 33.8            | 32.9            |  |
| Week 5 (n=73,74,73)               | 54.8             | 56.8            | 42.5            |  |
| Week 9 (n=73,74,73)               | 49.3             | 60.8            | 58.9            |  |
| Week 13 (n=73,74,73)              | 50.7             | 70.3            | 63              |  |
| Week 17 (n=73,74,73)              | 54.8             | 67.6            | 67.1            |  |
| Week 21 (n=72,74,72)              | 54.2             | 62.2            | 69.4            |  |
| Week 25 (EOT; n=62,63,62)         | 50               | 60.3            | 71              |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Participants with ACR 70% Improvement (ACR70) Response by Visit**

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with ACR 70% Improvement (ACR70) Response by Visit |
|-----------------|---|

## End point description:

ACR70 response:  $\geq$ 70% improvement in tender joint count;  $\geq$ 70% improvement in swollen joint count; and  $\geq$ 70% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. Non-responder imputation categorised participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

|  |           |
|--|-----------|
| End point type                         | Secondary |
| End point timeframe:                   |           |
| Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT) |           |

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           |                  |                 |                 |  |
| Week 3 (n=73,74,73)               | 2.7              | 2.7             | 2.7             |  |
| Week 5 (n=73,74,73)               | 6.8              | 6.8             | 8.2             |  |
| Week 9 (n=73,74,73)               | 12.3             | 17.6            | 16.4            |  |
| Week 13 (n=73,74,73)              | 19.2             | 28.4            | 20.5            |  |
| Week 17 (n=73,74,73)              | 15.1             | 18.9            | 19.2            |  |
| Week 21 (n=72,74,72)              | 13.9             | 23              | 20.8            |  |
| Week 25 (EOT; n=62,63,62)         | 16.1             | 17.5            | 19.4            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with ACR 50% Improvement (ACR50) Response by Visit

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with ACR 50% Improvement (ACR50) Response by Visit |
|-----------------|---|

End point description:

ACR50 response:  $\geq 50\%$  improvement in tender joint count;  $\geq 50\%$  improvement in swollen joint count; and  $\geq 50\%$  improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. Non-responder imputation categorized participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

|  |           |
|--|-----------|
| End point type                         | Secondary |
| End point timeframe:                   |           |
| Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT) |           |

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           |                  |                 |                 |  |
| Week 3 (n=73,74,73)               | 8.2              | 5.4             | 9.6             |  |
| Week 5 (n=73,74,73)               | 19.2             | 16.2            | 20.5            |  |

|                           |      |      |      |  |
|---------------------------|------|------|------|--|
| Week 9 (n=73,74,73)       | 21.9 | 32.4 | 35.6 |  |
| Week 13 (n=73,74,73)      | 35.6 | 40.5 | 31.5 |  |
| Week 17 (n=73,74,73)      | 24.7 | 36.5 | 37   |  |
| Week 21 (n=72,74,72)      | 27.8 | 37.8 | 38.9 |  |
| Week 25 (EOT; n=62,63,62) | 21   | 38.1 | 33.9 |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants by Anti-drug Antibody (ADA) Status

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants by Anti-drug Antibody (ADA) Status |
|-----------------|---|

End point description:

Presence of anti-rituximab antibodies in blood. Participants with a positive antibody status at any time during the study were defined as having overall positive antibody status; participants with a negative antibody status throughout the study were defined as having overall negative antibody status. mITT populations.

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

End point timeframe:

Days 1 (pre-dose), 15 (prior to infusion), 29, 57, 85, and 169.

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           | 9.6              | 13.5            | 12.3            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Neutralizing Antibody (NAb) in Participants with a Positive ADA by Visit

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Neutralizing Antibody (NAb) in Participants with a Positive ADA by Visit |
|-----------------|--|

End point description:

mITT population. Only participants with a positive ADA status were included in the analysis.

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

End point timeframe:

Days 1 (pre-dose), 15 (prior to infusion), 29, 57, 85, and 169.

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 35               | 39              | 34              |  |
| Units: Percentage of participants |                  |                 |                 |  |
| number (not applicable)           | 0                | 0               | 0               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Baseline and Change from Baseline in Disease Activity Score Based on 28-Joint Count and CRP (DAS28-CRP)

|                 |   |
|-----------------|---|
| End point title | Baseline and Change from Baseline in Disease Activity Score Based on 28-Joint Count and CRP (DAS28-CRP) |
|-----------------|---|

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP less than or equal to ( $\leq$ ) 3.2 implied low disease activity, DAS28-CRP greater than ( $>$ )3.2 to  $\leq$ 5.1 implied moderate to high disease activity, and DAS28-CRP less than ( $<$ )2.6 implied remission. mITT population.

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

End point timeframe:

Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                     | Rituximab-Pfizer        | Rituximab-EU           | Rituximab-US            |  |
|--------------------------------------|-------------------------|------------------------|-------------------------|--|
| Subject group type                   | Reporting group         | Reporting group        | Reporting group         |  |
| Number of subjects analysed          | 73                      | 74                     | 73                      |  |
| Units: Score on a scale              |                         |                        |                         |  |
| arithmetic mean (standard deviation) |                         |                        |                         |  |
| Baseline (n=73,74,73)                | 5.6862 ( $\pm$ 0.85109) | 5.7928 ( $\pm$ 0.9503) | 6.2221 ( $\pm$ 0.88162) |  |
| Week 3 (n=69,74,69)                  | -0.9 ( $\pm$ 1.01)      | -0.8 ( $\pm$ 1.13)     | -1.1 ( $\pm$ 1.02)      |  |
| Week 5 (n=71,71,67)                  | -1.4 ( $\pm$ 1.17)      | -1.4 ( $\pm$ 1.06)     | -1.6 ( $\pm$ 1.2)       |  |
| Week 9 (n=68,73,70)                  | -1.7 ( $\pm$ 1.29)      | -1.8 ( $\pm$ 1.3)      | -2.1 ( $\pm$ 1.37)      |  |
| Week 13 (n=67,72,67)                 | -2 ( $\pm$ 1.43)        | -2.1 ( $\pm$ 1.33)     | -2.3 ( $\pm$ 1.34)      |  |
| Week 17 (n=66,71,67)                 | -2 ( $\pm$ 1.32)        | -2.1 ( $\pm$ 1.39)     | -2.4 ( $\pm$ 1.35)      |  |
| Week 21 (n=60,65,59)                 | -2 ( $\pm$ 1.28)        | -1.9 ( $\pm$ 1.33)     | -2.6 ( $\pm$ 1.35)      |  |
| Week 25 (EOT; n=50,58,55)            | -1.7 ( $\pm$ 1.25)      | -2 ( $\pm$ 1.3)        | -2.5 ( $\pm$ 1.3)       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: % Change from Baseline in DAS28-CRP by Visit

|   |  |
|---|--|
| End point title   | % Change from Baseline in DAS28-CRP by Visit |
| End point description:<br>DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP $\leq 3.2$ implied low disease activity, DAS28-CRP $> 3.2$ to $\leq 5.1$ implied moderate to high disease activity, and DAS28-CRP $< 2.6$ implied remission. mITT population. |  |
| End point type  | Secondary                                    |
| End point timeframe:<br>Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)   |  |

| End point values                     | Rituximab-Pfizer     | Rituximab-EU         | Rituximab-US         |  |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      |  |
| Number of subjects analysed          | 73                   | 74                   | 73                   |  |
| Units: % change from baseline        |                      |                      |                      |  |
| arithmetic mean (standard deviation) |                      |                      |                      |  |
| Week 3 (n= 69, 74, 69)               | -16.1 ( $\pm$ 19.08) | -13.6 ( $\pm$ 20.41) | -18.6 ( $\pm$ 17.63) |  |
| Week 5 (n= 71, 71, 67)               | -25.4 ( $\pm$ 20.74) | -24 ( $\pm$ 18.22)   | -26 ( $\pm$ 21.88)   |  |
| Week 9 (n= 68, 73, 70)               | -31.2 ( $\pm$ 22.31) | -31 ( $\pm$ 21.92)   | -34.2 ( $\pm$ 22.97) |  |
| Week 13 (n= 67, 72, 67)              | -34.7 ( $\pm$ 24)    | -36.9 ( $\pm$ 22.1)  | -37.4 ( $\pm$ 21.42) |  |
| Week 17 (n= 66, 71, 67)              | -34.9 ( $\pm$ 22.65) | -35.4 ( $\pm$ 23.28) | -39.1 ( $\pm$ 21.35) |  |
| Week 21 (n= 60, 65, 59)              | -35.5 ( $\pm$ 21.99) | -33.4 ( $\pm$ 22.56) | 43.2 ( $\pm$ 21.39)  |  |
| Week 25 EOT (n= 50, 58, 55)          | -31.1 ( $\pm$ 22.72) | -34.6 ( $\pm$ 22.25) | -40 ( $\pm$ 20.55)   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Good European League Against Rheumatism (EULAR) Response Based on DAS28 by Visit

|   |  |
|---|--|
| End point title   | Percentage of Participants with Good European League Against Rheumatism (EULAR) Response Based on DAS28 by Visit |
| End point description:<br>The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline $> 1.2$ with DAS28 $\leq 3.2$ ; moderate responders: change from baseline $> 1.2$ with DAS28 $> 3.2$ to $\leq 5.1$ or change from baseline $> 0.6$ to $\leq 1.2$ with DAS28 $\leq 5.1$ ; non-responders: change from baseline $\leq 0.6$ , or change from baseline $> 0.6$ and $\leq 1.2$ with DAS28 $> 5.1$ . mITT population |  |
| End point type  | Secondary  |
| End point timeframe:<br>Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)  |  |



| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of participants |                  |                 |                 |  |
| number (not applicable)           |                  |                 |                 |  |
| Week 3 (n= 69, 74, 69)            | 14.5             | 10.8            | 8.7             |  |
| Week 5 (n=71, 71, 67)             | 22.5             | 22.5            | 19.4            |  |
| Week 9 (n= 68, 73, 70)            | 30.9             | 31.5            | 25.7            |  |
| Week 13 (n= 67, 72, 67)           | 41.8             | 44.4            | 32.8            |  |
| Week 17 (n= 66, 71, 67)           | 36.4             | 38              | 32.8            |  |
| Week 21 (n= 60, 65, 59)           | 35               | 35.4            | 47.5            |  |
| Week 25 EOT (n= 50, 58, 55)       | 30               | 36.2            | 41.8            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Moderate EULAR Response Based on Disease Activity Score Based on DAS28 by Visit

|  |   |
|--|---|
| End point title  | Percentage of Participants with Moderate EULAR Response Based on Disease Activity Score Based on DAS28 by Visit |
| End point description:   |   |
| The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline $>1.2$ with DAS28 $\leq 3.2$ ; moderate responders: change from baseline $>1.2$ with DAS28 $>3.2$ to $\leq 5.1$ or change from baseline $>0.6$ to $\leq 1.2$ with DAS28 $\leq 5.1$ ; non-responders: change from baseline $\leq 0.6$ , or change from baseline $>0.6$ and $\leq 1.2$ with DAS28 $>5.1$ . mITT population. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)   |   |

| End point values            | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------|------------------|-----------------|-----------------|--|
| Subject group type          | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed | 73               | 74              | 73              |  |
| Units: % of participants    |                  |                 |                 |  |
| number (not applicable)     |                  |                 |                 |  |
| Week 3 (n= 69, 74, 69)      | 33.3             | 35.1            | 42              |  |
| Week 5 (n= 71, 71, 67)      | 47.9             | 39.4            | 43.3            |  |
| Week 9 (n= 68, 73, 70)      | 45.6             | 43.8            | 54.3            |  |
| Week 13 (n= 67, 72, 67)     | 38.8             | 37.5            | 44.8            |  |
| Week 17 (n= 66, 71, 67)     | 45.5             | 39.4            | 53.7            |  |
| Week 21 (n= 60, 65, 59)     | 51.7             | 46.2            | 39              |  |

|                             |    |      |      |  |
|-----------------------------|----|------|------|--|
| Week 25 EOT (n= 50, 58, 55) | 50 | 46.6 | 43.6 |  |
|-----------------------------|----|------|------|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with No EULAR Response Based on DAS28 by Visit

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with No EULAR Response Based on DAS28 by Visit |
|-----------------|---|

End point description:

The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline  $>1.2$  with DAS28  $\leq 3.2$ ; moderate responders: change from baseline  $>1.2$  with DAS28  $>3.2$  to  $\leq 5.1$  or change from baseline  $>0.6$  to  $\leq 1.2$  with DAS28  $\leq 5.1$ ; non-responders: change from baseline  $\leq 0.6$ , or change from baseline  $>0.6$  and  $\leq 1.2$  with DAS28  $>5.1$ . mITT population.

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

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values            | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------|------------------|-----------------|-----------------|--|
| Subject group type          | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed | 73               | 74              | 73              |  |
| Units: % of participants    |                  |                 |                 |  |
| number (not applicable)     |                  |                 |                 |  |
| Week 3 (n= 69, 74, 69)      | 52.2             | 54.1            | 49.3            |  |
| Week 5 (n= 71, 71, 67)      | 29.6             | 38              | 37.3            |  |
| Week 9 (n= 68, 73, 70)      | 23.5             | 24.7            | 20              |  |
| Week 13 (n= 67, 72, 67)     | 19.4             | 18.1            | 22.4            |  |
| Week 17 (n= 66, 71, 67)     | 18.2             | 22.5            | 13.4            |  |
| Week 21 (n= 60, 65, 59)     | 13.3             | 18.5            | 13.6            |  |
| Week 25 EOT (n= 50, 58, 55) | 20               | 17.2            | 14.5            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Low Disease Activity Score (DAS; $\leq 3.2$ ) by Visit

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Low Disease Activity Score (DAS; $\leq 3.2$ ) by Visit |
|-----------------|--|

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP  $\leq 3.2$  implied low disease activity. mITT population.

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

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values            | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------|------------------|-----------------|-----------------|--|
| Subject group type          | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed | 73               | 74              | 73              |  |
| Units: % of participants    |                  |                 |                 |  |
| number (not applicable)     |                  |                 |                 |  |
| Week 3 (n=69,74,69)         | 14.5             | 10.8            | 10.1            |  |
| Week 5 (n=71,71,67)         | 23.9             | 25.4            | 19.4            |  |
| Week 9 (68,73,70)           | 30.9             | 32.9            | 25.7            |  |
| Week 13 (n=67,72,67)        | 41.8             | 44.4            | 32.8            |  |
| Week 17 (n=66,71,67)        | 36.4             | 38              | 32.8            |  |
| Week 21 (n=60,65,59)        | 35               | 36.9            | 47.5            |  |
| Week 25 (EOT; n=50,58,55)   | 32               | 37.9            | 41.8            |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 3 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-EU                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 0.75   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.31   |
| upper limit                             | 1.78   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 3 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.7             |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.28            |
| upper limit                             | 1.73            |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 3 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 0.94                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.36                                       |
| upper limit                             | 2.45                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 5 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-EU                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 1.06   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.6  |
| upper limit                             | 1.88   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 5 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.81            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.43            |
| upper limit                             | 1.54            |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 5 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 0.77                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.41                                       |
| upper limit                             | 1.44                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 9 |
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 1.06   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.66   |
| upper limit                             | 1.73   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 9 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.83            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.49            |
| upper limit                             | 1.42            |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 9 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 0.78                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.47                                       |
| upper limit                             | 1.31                                       |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 13 |
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 1.06  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.73  |
| upper limit                             | 1.56  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 13 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.79            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.5             |
| upper limit                             | 1.22            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 13 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 0.74  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.48  |
| upper limit                             | 1.13  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 17 |
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 1.05  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.68  |
| upper limit                             | 1.62  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 17 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.9             |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.57            |
| upper limit                             | 1.44            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 17 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 0.86  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.55  |
| upper limit                             | 1.36  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 21 |
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 1.05  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.66  |
| upper limit                             | 1.69  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 21 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                 |



|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.36            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.88            |
| upper limit                             | 2.1             |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 21 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 1.29  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.85  |
| upper limit                             | 1.95  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 25 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 1.19  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.7   |
| upper limit                             | 2   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-US versus rituximab-Pfizer at Week 25 |
| Comparison groups                 | Rituximab-US v Rituximab-Pfizer                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 146             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.31            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.78            |
| upper limit                             | 2.18            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 25 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 1.1   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.7   |
| upper limit                             | 1.73  |

## Secondary: Percentage of Participants with DAS Remission (DAS <2.6) by Visit

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with DAS Remission (DAS <2.6) by Visit |
|-----------------|---|

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP <2.6 implied remission. mITT population.

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

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

| End point values                  | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|-----------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed       | 73               | 74              | 73              |  |
| Units: Percentage of Participants |                  |                 |                 |  |
| number (not applicable)           |                  |                 |                 |  |
| Week 3 (n=69,74,69)               | 8.7              | 4.1             | 7.2             |  |
| Week 5 (n=71,71,67)               | 16.9             | 8.5             | 11.9            |  |
| Week 9 (n=68,73,70)               | 26.5             | 20.5            | 20              |  |
| Week 13 (n=67,72,67)              | 28.4             | 29.2            | 25.4            |  |

|                           |      |      |      |  |
|---------------------------|------|------|------|--|
| Week 17 (n=66,71,67)      | 25.8 | 25.4 | 23.9 |  |
| Week 21 (n=60,65,59)      | 25   | 16.9 | 30.5 |  |
| Week 25 (EOT; n=50,58,55) | 28   | 24.1 | 23.6 |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 3 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-EU                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 0.47   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.12   |
| upper limit                             | 1.79   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 3 |
| Comparison groups                       | Rituximab-US v Rituximab-Pfizer                |
| Number of subjects included in analysis | 146  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 0.83   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.27   |
| upper limit                             | 2.6  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 3 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 1.79                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.44                                       |
| upper limit                             | 7.2  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-EU versus rituximab-Pfizer at Week 5 |
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 0.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.2  |
| upper limit                             | 1.26   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 5 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-US                |
| Number of subjects included in analysis | 146  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Log risk ratio                                 |
| Point estimate                          | 0.71   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.31   |
| upper limit                             | 1.62   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 5 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 1.41                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.52                                       |
| upper limit                             | 3.86                                       |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Rituximab-EU versus rituximab-Pfizer at Week 9 |
|-----------------------------------|--|

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | Rituximab-EU v Rituximab-Pfizer |
| Number of subjects included in analysis | 147                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority                 |
| Parameter estimate                      | Risk ratio (RR)                 |
| Point estimate                          | 0.78                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.43                            |
| upper limit                             | 1.41                            |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 9 |
| Comparison groups                       | Rituximab-US v Rituximab-Pfizer                |
| Number of subjects included in analysis | 146  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | non-inferiority                                |
| Parameter estimate                      | Risk ratio (RR)                                |
| Point estimate                          | 0.76   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.41   |
| upper limit                             | 1.4  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 9 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                |
| Number of subjects included in analysis | 147  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority                            |
| Parameter estimate                      | Risk ratio (RR)                            |
| Point estimate                          | 0.97                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.51                                       |
| upper limit                             | 1.87                                       |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-EU versus rituximab-Pfizer at Week 13 |
| Comparison groups                 | Rituximab-EU v Rituximab-Pfizer                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 147             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 1.03            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.61            |
| upper limit                             | 1.74            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 13 |
| Comparison groups                       | Rituximab-US v Rituximab-Pfizer                 |
| Number of subjects included in analysis | 146   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 0.89  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.51  |
| upper limit                             | 1.57  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 13 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 0.87  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.5   |
| upper limit                             | 1.5   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-EU versus rituximab-Pfizer at Week 17 |
| Comparison groups                 | Rituximab-Pfizer v Rituximab-EU                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 147             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.98            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.56            |
| upper limit                             | 1.74            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 17 |
| Comparison groups                       | Rituximab-US v Rituximab-Pfizer                 |
| Number of subjects included in analysis | 146   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 0.93  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.51  |
| upper limit                             | 1.68  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 17 |
| Comparison groups                       | Rituximab-US v Rituximab-EU                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 0.94  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.52  |
| upper limit                             | 1.69  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-EU versus rituximab-Pfizer at Week 21 |
| Comparison groups                 | Rituximab-EU v Rituximab-Pfizer                 |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 147             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.68            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.34            |
| upper limit                             | 1.36            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 21 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-US                 |
| Number of subjects included in analysis | 146   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 1.22  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.68  |
| upper limit                             | 2.19  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 21 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Risk ratio (RR)                             |
| Point estimate                          | 1.8   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.93  |
| upper limit                             | 3.5   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Rituximab-EU versus rituximab-Pfizer at Week 25 |
| Comparison groups                 | Rituximab-Pfizer v Rituximab-EU                 |



|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 147             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| Parameter estimate                      | Risk ratio (RR) |
| Point estimate                          | 0.86            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.46            |
| upper limit                             | 1.63            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-Pfizer at Week 25 |
| Comparison groups                       | Rituximab-Pfizer v Rituximab-US                 |
| Number of subjects included in analysis | 146   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | non-inferiority                                 |
| Parameter estimate                      | Risk ratio (RR)                                 |
| Point estimate                          | 0.84  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.44  |
| upper limit                             | 1.62  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Rituximab-US versus rituximab-EU at Week 25 |
| Comparison groups                       | Rituximab-EU v Rituximab-US                 |
| Number of subjects included in analysis | 147   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | non-inferiority                             |
| Parameter estimate                      | Log risk ratio                              |
| Point estimate                          | 0.98  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.51  |
| upper limit                             | 1.89  |

## Secondary: Baseline and Change from Baseline in HAQ-DI by Visit

|                 |  |
|-----------------|--|
| End point title | Baseline and Change from Baseline in HAQ-DI by Visit |
|-----------------|--|

End point description:

Health Assessment Questionnaire - Disability Index (HAQ-DI): participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total

possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. mITT population.

|   |           |
|---|-----------|
| End point type                                      | Secondary |
| End point timeframe:                                |           |
| Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT) |           |

| End point values                     | Rituximab-Pfizer  | Rituximab-EU       | Rituximab-US       |  |
|--------------------------------------|-------------------|--------------------|--------------------|--|
| Subject group type                   | Reporting group   | Reporting group    | Reporting group    |  |
| Number of subjects analysed          | 73                | 74                 | 73                 |  |
| Units: Scores on a scale             |                   |                    |                    |  |
| arithmetic mean (standard deviation) |                   |                    |                    |  |
| Baseline (n=73,74,73)                | 1.6541 (± 0.5734) | 1.5929 (± 0.53597) | 1.7466 (± 0.62081) |  |
| Week 3 (n=70,74,70)                  | -0.2 (± 0.39)     | -0.2 (± 0.34)      | -0.2 (± 0.33)      |  |
| Week 5 (n=72,70,68)                  | -0.3 (± 0.39)     | -0.3 (± 0.45)      | -0.3 (± 0.43)      |  |
| Week 9 (n=68,73,70)                  | -0.4 (± 0.47)     | -0.5 (± 0.5)       | -0.5 (± 0.54)      |  |
| Week 13 (n=67,72,68)                 | -0.4 (± 0.55)     | -0.6 (± 0.56)      | -0.5 (± 0.52)      |  |
| Week 17 (n=66,71,67)                 | -0.3 (± 0.49)     | -0.6 (± 0.58)      | -0.5 (± 0.55)      |  |
| Week 21 (n=63,70,64)                 | -0.4 (± 0.53)     | -0.6 (± 0.58)      | -0.6 (± 0.61)      |  |
| Week 25 (EOT; n=52,59,55)            | -0.4 (± 0.49)     | -0.5 (± 0.63)      | -0.6 (± 0.57)      |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in HAQ-DI Score by Visit

|   |   |
|---|---|
| End point title   | Percent Change from Baseline in HAQ-DI Score by Visit |
| End point description:  |   |
| HAQ-DI: participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. mITT population. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)   |   |

| End point values                     | Rituximab-Pfizer | Rituximab-EU    | Rituximab-US    |  |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group  | Reporting group | Reporting group |  |
| Number of subjects analysed          | 72               | 74              | 73              |  |
| Units: Percentage change             |                  |                 |                 |  |
| arithmetic mean (standard deviation) |                  |                 |                 |  |
| Week 3 (n=70,74,70)                  | -10.4 (± 37.27)  | -13.2 (± 26.03) | -9 (± 25.68)    |  |

|                           |                 |                 |                 |  |
|---------------------------|-----------------|-----------------|-----------------|--|
| Week 5 (n=72,70,68)       | -15.1 (± 40)    | -23.5 (± 30.45) | -14.8 (± 43.82) |  |
| Week 9 (n=68,73,70)       | -22.4 (± 35.96) | -31.7 (± 34.64) | -24.5 (± 35.51) |  |
| Week 13 (n=67,72,68)      | -14.6 (± 50.35) | -39.5 (± 37.46) | -30.7 (± 31.91) |  |
| Week 17 (n=66,71,67)      | -16.9 (± 48.95) | -39.1 (± 38.85) | -28.8 (± 36.43) |  |
| Week 21 (n=63,70,64)      | -21 (± 48.04)   | -39.2 (± 38.34) | -33.5 (± 35.18) |  |
| Week 25 (EOT; n=52,59,55) | -17.7 (± 54.01) | -37.1 (± 41.18) | -38.4 (± 34.6)  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected for 28 days after the last administration of study drug or, in the case of incomplete B-cell count recovery, for up to 1 year after Study Day 1.

Adverse event reporting additional description:

The same event may appear as both an AE and a serious AE (SAE). However, what is presented are distinct events. An event may be categorized as serious in 1 participant and as non-serious in another participant, or 1 participant may have experienced both a serious and non-serious event during the study.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Rituximab-Pfizer |
|-----------------------|------------------|

Reporting group description:

Rituximab-Pfizer group received intravenous (IV) rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 milliliters (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Rituximab-US |
|-----------------------|--------------|

Reporting group description:

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Rituximab-EU |
|-----------------------|--------------|

Reporting group description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

| Serious adverse events  | Rituximab-Pfizer | Rituximab-US   | Rituximab-EU   |
|---|------------------|----------------|----------------|
| Total subjects affected by serious adverse events                   |                  |                |                |
| subjects affected / exposed   | 5 / 73 (6.85%)   | 4 / 73 (5.48%) | 2 / 74 (2.70%) |
| number of deaths (all causes)                                       | 1                | 0              | 0              |
| number of deaths resulting from adverse events                      |                  |                |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                |                |
| Bone neoplasm   |                  |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (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          |
| Cardiac disorders                               |                |                |                |
| Atrial flutter                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (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          |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (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          |
| Cardiac failure congestive                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (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          |
| Pericarditis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Thrombocytopenic purpura                        |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Intentional self-injury                         |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthropathy                                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (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          |
| <b>Infections and infestations</b>              |                |                |                |
| Arthritis bacterial                             |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (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          |
| Bacterial sepsis                                |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (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          |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (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          |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>  | Rituximab-Pfizer | Rituximab-US     | Rituximab-EU     |
|--|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events                      |                  |                  |                  |
| subjects affected / exposed  | 50 / 73 (68.49%) | 45 / 73 (61.64%) | 40 / 74 (54.05%) |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                  |                  |                  |
| Basal cell carcinoma   |                  |                  |                  |
| subjects affected / exposed  | 0 / 73 (0.00%)   | 0 / 73 (0.00%)   | 1 / 74 (1.35%)   |
| occurrences (all)  | 0                | 0                | 1                |
| Benign neoplasm of thyroid gland   |                  |                  |                  |
| subjects affected / exposed  | 1 / 73 (1.37%)   | 0 / 73 (0.00%)   | 0 / 74 (0.00%)   |
| occurrences (all)  | 1                | 0                | 0                |
| Skin papilloma   |                  |                  |                  |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 0 / 73 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 |
| Vascular disorders                                      |                     |                     |                     |
| Flushing  |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 0 / 73 (0.00%)      | 1 / 74 (1.35%)      |
| occurrences (all)                                       | 0                   | 0                   | 2                   |
| Hot flush   |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 1 / 73 (1.37%)      | 1 / 74 (1.35%)      |
| occurrences (all)                                       | 0                   | 1                   | 1                   |
| Hypertension  |                     |                     |                     |
| subjects affected / exposed                             | 4 / 73 (5.48%)      | 1 / 73 (1.37%)      | 2 / 74 (2.70%)      |
| occurrences (all)                                       | 4                   | 1                   | 2                   |
| Hypotension   |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 0 / 73 (0.00%)      | 1 / 74 (1.35%)      |
| occurrences (all)                                       | 0                   | 0                   | 1                   |
| Peripheral arterial occlusive disease                   |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 1 / 73 (1.37%)      | 0 / 74 (0.00%)      |
| occurrences (all)                                       | 0                   | 1                   | 0                   |
| Venous insufficiency                                    |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 1 / 73 (1.37%)      | 0 / 74 (0.00%)      |
| occurrences (all)                                       | 0                   | 1                   | 0                   |
| General disorders and administration<br>site conditions |                     |                     |                     |
| Adverse drug reaction                                   |                     |                     |                     |
| subjects affected / exposed                             | 0 / 73 (0.00%)      | 1 / 73 (1.37%)      | 0 / 74 (0.00%)      |
| occurrences (all)                                       | 0                   | 1                   | 0                   |
| Asthenia  |                     |                     |                     |
| subjects affected / exposed                             | 3 / 73 (4.11%)      | 0 / 73 (0.00%)      | 0 / 74 (0.00%)      |
| occurrences (all)                                       | 3                   | 0                   | 0                   |
| Chest discomfort  |                     |                     |                     |
| subjects affected / exposed                             | 1 / 73 (1.37%)      | 0 / 73 (0.00%)      | 1 / 74 (1.35%)      |
| occurrences (all)                                       | 1                   | 0                   | 1                   |
| Fatigue   |                     |                     |                     |
| subjects affected / exposed                             | 5 / 73 (6.85%)      | 1 / 73 (1.37%)      | 1 / 74 (1.35%)      |
| occurrences (all)                                       | 7                   | 1                   | 2                   |
| Inflammation  |                     |                     |                     |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Infusion site extravasation                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Local swelling                                  |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Mucosal inflammation                            |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Oedema peripheral                               |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                               | 1              | 0              | 1              |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Immune system disorders                         |                |                |                |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                               | 1              | 0              | 1              |
| Reproductive system and breast disorders        |                |                |                |
| Prostatomegaly                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Vaginal haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Acute pulmonary oedema                          |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Cough   |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Dry throat                                      |                |                |                |



|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Dyspnoea                     |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 3 / 73 (4.11%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 3              | 0              |
| Hypoxia                      |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Nasal congestion             |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Oropharyngeal pain           |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Productive cough             |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Pulmonary congestion         |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Rales                        |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 2 / 73 (2.74%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 2              | 0              |
| Respiratory disorder         |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Respiratory tract congestion |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Rhinorrhoea                  |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Sneezing                     |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Sputum discoloured           |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 73 (1.37%)<br>1 | 2 / 73 (2.74%)<br>2 | 1 / 74 (1.35%)<br>1 |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Psychiatric disorders  |                     |                     |                     |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 73 (0.00%)<br>0 | 3 / 73 (4.11%)<br>4 | 1 / 74 (1.35%)<br>1 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 73 (2.74%)<br>2 | 3 / 73 (4.11%)<br>3 | 1 / 74 (1.35%)<br>1 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 73 (1.37%)<br>1 | 3 / 73 (4.11%)<br>3 | 2 / 74 (2.70%)<br>2 |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 73 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 |
| Investigations   |                     |                     |                     |
| Bilirubin conjugated increased<br>subjects affected / exposed<br>occurrences (all)       | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 73 (1.37%)<br>1 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Blood calcium increased  |                     |                     |                     |

|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)            | 0              | 0              | 1              |
| Blood creatinine increased   |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Blood glucose increased      |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Blood potassium decreased    |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Blood pressure decreased     |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Blood pressure increased     |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 2 / 74 (2.70%) |
| occurrences (all)            | 0              | 0              | 2              |
| Blood urea increased         |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 1 / 74 (1.35%) |
| occurrences (all)            | 0              | 1              | 1              |
| Haematocrit decreased        |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Haemoglobin decreased        |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Liver function test abnormal |                |                |                |
| subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Lymphocyte count decreased   |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Neutrophil count decreased   |                |                |                |
| subjects affected / exposed  | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Weight decreased             |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| White blood cell count decreased               |                |                |                |
| subjects affected / exposed                    | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Arthropod bite                                 |                |                |                |
| subjects affected / exposed                    | 2 / 73 (2.74%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 2              | 1              | 0              |
| Epicondylitis                                  |                |                |                |
| subjects affected / exposed                    | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Fall   |                |                |                |
| subjects affected / exposed                    | 1 / 73 (1.37%) | 2 / 73 (2.74%) | 1 / 74 (1.35%) |
| occurrences (all)                              | 1              | 2              | 1              |
| Foot fracture                                  |                |                |                |
| subjects affected / exposed                    | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Fractured sacrum                               |                |                |                |
| subjects affected / exposed                    | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Hand fracture                                  |                |                |                |
| subjects affected / exposed                    | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Infusion related reaction                      |                |                |                |
| subjects affected / exposed                    | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Laceration                                     |                |                |                |
| subjects affected / exposed                    | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Ligament sprain                                |                |                |                |
| subjects affected / exposed                    | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Limb injury                                    |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 1              | 0              | 1              |
| Lumbar vertebral fracture   |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Muscle contusion            |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Nail avulsion               |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Tooth fracture              |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Underdose                   |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Vaccination complication    |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Wound                       |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Cardiac disorders           |                |                |                |
| Atrial fibrillation         |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Atrial flutter              |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Extrasystoles               |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Tachycardia paroxysmal      |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| Nervous system disorders             |                |                |                |
| Dizziness                            |                |                |                |
| subjects affected / exposed          | 2 / 73 (2.74%) | 2 / 73 (2.74%) | 1 / 74 (1.35%) |
| occurrences (all)                    | 2              | 2              | 1              |
| Headache                             |                |                |                |
| subjects affected / exposed          | 3 / 73 (4.11%) | 4 / 73 (5.48%) | 2 / 74 (2.70%) |
| occurrences (all)                    | 5              | 4              | 2              |
| Hypoaesthesia                        |                |                |                |
| subjects affected / exposed          | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Lethargy                             |                |                |                |
| subjects affected / exposed          | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                    | 1              | 0              | 1              |
| Migraine                             |                |                |                |
| subjects affected / exposed          | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 1              | 1              | 0              |
| Neuralgia                            |                |                |                |
| subjects affected / exposed          | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 2              | 0              | 0              |
| Paraesthesia                         |                |                |                |
| subjects affected / exposed          | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Sciatica                             |                |                |                |
| subjects affected / exposed          | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 2              | 0              | 0              |
| Sinus headache                       |                |                |                |
| subjects affected / exposed          | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Syncope                              |                |                |                |
| subjects affected / exposed          | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Blood and lymphatic system disorders |                |                |                |
| Anaemia                              |                |                |                |
| subjects affected / exposed          | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Iron deficiency anaemia              |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Thrombocytopenia            |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Ear and labyrinth disorders |                |                |                |
| Cerumen impaction           |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Ear disorder                |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Ear pain                    |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Ear pruritus                |                |                |                |
| subjects affected / exposed | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Tinnitus                    |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Vertigo positional          |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Eye disorders               |                |                |                |
| Abnormal sensation in eye   |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 2              |
| Blepharitis                 |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Conjunctivitis allergic     |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Dry eye                     |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Eye haemorrhage             |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Eye pain                    |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Eye pruritus                |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Eyelid pain                 |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Gastrointestinal disorders  |                |                |                |
| Abdominal distension        |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 73 (2.74%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Abdominal pain              |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 73 (2.74%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 3              | 0              |
| Abdominal pain lower        |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Abdominal pain upper        |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Abdominal tenderness        |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Colitis ulcerative          |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Constipation                |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 2 / 74 (2.70%) |
| occurrences (all)           | 1              | 1              | 2              |



|                                  |                |                |                |
|----------------------------------|----------------|----------------|----------------|
| Diarrhoea                        |                |                |                |
| subjects affected / exposed      | 1 / 73 (1.37%) | 2 / 73 (2.74%) | 2 / 74 (2.70%) |
| occurrences (all)                | 1              | 3              | 2              |
| Diverticulum                     |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                | 0              | 0              | 1              |
| Diverticulum intestinal          |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                | 0              | 0              | 1              |
| Dry mouth                        |                |                |                |
| subjects affected / exposed      | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 2 / 74 (2.70%) |
| occurrences (all)                | 2              | 0              | 2              |
| Dyspepsia                        |                |                |                |
| subjects affected / exposed      | 2 / 73 (2.74%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                | 2              | 1              | 0              |
| Dysphagia                        |                |                |                |
| subjects affected / exposed      | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                | 1              | 0              | 1              |
| Gastrooesophageal reflux disease |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 1 / 74 (1.35%) |
| occurrences (all)                | 0              | 1              | 1              |
| Haematochezia                    |                |                |                |
| subjects affected / exposed      | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                | 1              | 0              | 0              |
| Haemorrhoids                     |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                | 0              | 0              | 1              |
| Lip swelling                     |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Lip ulceration                   |                |                |                |
| subjects affected / exposed      | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                | 0              | 1              | 0              |
| Mouth ulceration                 |                |                |                |
| subjects affected / exposed      | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                | 1              | 0              | 0              |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Nausea                                 |                |                |                |
| subjects affected / exposed            | 1 / 73 (1.37%) | 4 / 73 (5.48%) | 1 / 74 (1.35%) |
| occurrences (all)                      | 1              | 5              | 1              |
| Rectal haemorrhage                     |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Stomatitis                             |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Tongue ulceration                      |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Vomiting                               |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 2 / 74 (2.70%) |
| occurrences (all)                      | 0              | 2              | 2              |
| Hepatobiliary disorders                |                |                |                |
| Hepatic steatosis                      |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Skin and subcutaneous tissue disorders |                |                |                |
| Campbell de Morgan spots               |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Dermatitis                             |                |                |                |
| subjects affected / exposed            | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Dermatitis contact                     |                |                |                |
| subjects affected / exposed            | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Dry skin                               |                |                |                |
| subjects affected / exposed            | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Eczema                                 |                |                |                |
| subjects affected / exposed            | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Erythema                               |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Intertrigo                  |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Onycholysis                 |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Pruritus                    |                |                |                |
| subjects affected / exposed | 3 / 73 (4.11%) | 2 / 73 (2.74%) | 1 / 74 (1.35%) |
| occurrences (all)           | 3              | 2              | 1              |
| Rash                        |                |                |                |
| subjects affected / exposed | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 3              | 0              | 1              |
| Rash vesicular              |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Skin lesion                 |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 1              | 0              | 1              |
| Skin mass                   |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Urticaria                   |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 1 / 73 (1.37%) | 1 / 74 (1.35%) |
| occurrences (all)           | 1              | 1              | 1              |
| Renal and urinary disorders |                |                |                |
| Haematuria                  |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Hydronephrosis              |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Nephrolithiasis             |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Renal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 73 (1.37%)<br>1 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 3 / 73 (4.11%)<br>3 | 4 / 73 (5.48%)<br>4 | 4 / 74 (5.41%)<br>5 |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 73 (1.37%)<br>1 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 73 (1.37%)<br>1 | 2 / 73 (2.74%)<br>2 | 1 / 74 (1.35%)<br>1 |
| Bursitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Costochondritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Fibromyalgia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 73 (1.37%)<br>1 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Joint instability<br>subjects affected / exposed<br>occurrences (all)   | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)  | 2 / 73 (2.74%)<br>2 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Muscle atrophy  |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Muscle spasms               |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 1              | 0              | 1              |
| Musculoskeletal chest pain  |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Musculoskeletal discomfort  |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Musculoskeletal pain        |                |                |                |
| subjects affected / exposed | 4 / 73 (5.48%) | 0 / 73 (0.00%) | 2 / 74 (2.70%) |
| occurrences (all)           | 4              | 0              | 2              |
| Musculoskeletal stiffness   |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Myalgia                     |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Neck pain                   |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Osteoarthritis              |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Osteonecrosis               |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Pain in extremity           |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 73 (2.74%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 2              | 0              |
| Periarthritis               |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Rheumatoid arthritis        |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 73 (1.37%) | 5 / 73 (6.85%) | 5 / 74 (6.76%) |
| occurrences (all)           | 1              | 6              | 8              |
| Spinal pain                 |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Spondylolisthesis           |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Synovitis                   |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Infections and infestations |                |                |                |
| Acute sinusitis             |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Arthritis infective         |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |
| Bronchitis                  |                |                |                |
| subjects affected / exposed | 3 / 73 (4.11%) | 4 / 73 (5.48%) | 2 / 74 (2.70%) |
| occurrences (all)           | 3              | 4              | 2              |
| Cellulitis                  |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Ear infection               |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 1              | 0              | 1              |
| Furuncle                    |                |                |                |
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Gastroenteritis             |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 73 (2.74%) | 2 / 74 (2.70%) |
| occurrences (all)           | 0              | 2              | 2              |
| Gastroenteritis viral       |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 1              | 1              |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Gastrointestinal viral infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 |
| Herpes simplex<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Infected bites<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>2 | 0 / 74 (0.00%)<br>0 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 73 (2.74%)<br>2 | 2 / 73 (2.74%)<br>2 | 1 / 74 (1.35%)<br>1 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 73 (4.11%)<br>3 | 3 / 73 (4.11%)<br>3 | 1 / 74 (1.35%)<br>1 |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Otitis externa<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 73 (0.00%)<br>0 | 0 / 73 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 73 (1.37%)<br>1 | 0 / 73 (0.00%)<br>0 | 0 / 74 (0.00%)<br>0 |
| Respiratory tract infection viral<br>subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0 | 1 / 73 (1.37%)<br>1 | 0 / 74 (0.00%)<br>0 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Rhinitis                                |                |                |                |
| subjects affected / exposed             | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                       | 1              | 0              | 1              |
| Sinusitis                               |                |                |                |
| subjects affected / exposed             | 3 / 73 (4.11%) | 2 / 73 (2.74%) | 6 / 74 (8.11%) |
| occurrences (all)                       | 3              | 2              | 8              |
| Tooth abscess                           |                |                |                |
| subjects affected / exposed             | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 2 / 74 (2.70%) |
| occurrences (all)                       | 1              | 0              | 2              |
| Upper respiratory tract infection       |                |                |                |
| subjects affected / exposed             | 7 / 73 (9.59%) | 4 / 73 (5.48%) | 5 / 74 (6.76%) |
| occurrences (all)                       | 7              | 4              | 6              |
| Urinary tract infection                 |                |                |                |
| subjects affected / exposed             | 1 / 73 (1.37%) | 2 / 73 (2.74%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 2              | 2              | 0              |
| Viral infection                         |                |                |                |
| subjects affected / exposed             | 1 / 73 (1.37%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Viral upper respiratory tract infection |                |                |                |
| subjects affected / exposed             | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Metabolism and nutrition disorders      |                |                |                |
| Decreased appetite                      |                |                |                |
| subjects affected / exposed             | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Hypercholesterolaemia                   |                |                |                |
| subjects affected / exposed             | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Hyperglycaemia                          |                |                |                |
| subjects affected / exposed             | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 0 / 74 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Hyperlipidaemia                         |                |                |                |
| subjects affected / exposed             | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Hypokalaemia                            |                |                |                |



|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 73 (2.74%) | 0 / 73 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all)           | 4              | 0              | 0              |
| Type 2 diabetes mellitus    |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 73 (1.37%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 1              | 1              |
| Vitamin B12 deficiency      |                |                |                |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 73 (0.00%) | 1 / 74 (1.35%) |
| occurrences (all)           | 0              | 0              | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 12 January 2012   | The original protocol (dated 15 December 2011) was amended on 12 January 2012 with administrative changes. The purpose of this amendment was to correct typographical errors in the Schedule of Activities, References, and Appendices 6 and 7. Appendix 6 (Rescue Therapy) was removed to prevent confusion.   |
| 20 January 2012   | The protocol was amended on 20 January 2012 with administrative changes. The purpose of this amendment was to adjust terminology referencing biosimilarity and reference products per advice from US Food and Drug Administration (FDA).  |
| 02 February 2012  | The protocol was amended on 02 February 2012 with administrative changes. The purpose of this amendment was to adjust terminology referencing product licensure per advice from US FDA.   |
| 07 September 2012 | The protocol was amended on 07 September 2012 with administrative changes, including corrections to typographical errors and updates to section numbering along with clarifications/ corrections to the following sections of the protocol: Primary PK parameters, Schedule of Activities, PK/PD Study Sampling Time Points, Safety of Rituximab (Section 1.1.1.2), Rationale, PK Evaluations, Inclusion and Exclusion Criteria, Preparation and Dosing, Stable Background Pain or Other Arthritis Therapy, Pharmacokinetic Evaluation, Pharmacodynamic Evaluation, Per Protocol (PP) Population, Pharmacokinetic Analysis, Analysis of Clinical Response Endpoints, Interim Look, Concomitant Medications and Procedures.  |
| 22 August 2013    | The protocol was amended on 22 August 2013 with administrative changes, including corrections to typographical errors and updates to section numbering. Population PK/PD modelling was added as a secondary objective. Visit windows were clarified and inconsistencies within the protocol were corrected. It was clarified that tuberculosis screening should have been conducted per local guidelines and alternative radiological techniques to chest x-ray were acceptable. Updated language regarding interim PK assessment. Corrected dose to 1000 mg, rather than 1000 mg/kg. Updated sections regarding the timeframe for reporting AEs, occupational exposure, exposure during pregnancy, and communication of results to conform to current sponsor standard language. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported