



Clinical trial results:

A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of GP2013 and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or two anti- TNF therapies

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2010-021184-32 |
| Trial protocol | DE FR ES AT IT BE EE HU PL BG GB |
| Global end of trial date | 10 November 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 26 November 2017 |
| First version publication date | 26 November 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | GP13-201 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01274182 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Hexal AG |
| Sponsor organisation address | Industriestrasse 25, Holzkirchen, Germany, 83607 |
| Public contact | Strategic Planning Biopharma Clinical Development , Sandoz , 0049 80244760, biopharma.clinicaltrials@sandoz.com |
| Scientific contact | Strategic Planning Biopharma Clinical Development , Sandoz , 0049 80244760, biopharma.clinicaltrials@sandoz.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 September 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate bioequivalence between GP2013 and rituximab in combination with MTX in patients with active RA who have not responded adequately, or have shown intolerance, to DMARDs, including MTX, and one or two anti-TNF therapies. Bioequivalence is defined as AUC(0-inf) and Cmax of blood concentrations of the drugs being comparable, i.e. the 90% confidence interval for the ratio of the geometric means (GP2013/rituximab) estimated based on non-compartmental analysis based on assessments up to week 24 must be within the standard bioequivalence limits 0.8 to 1.25.

Protection of trial subjects:

This clinical study was designed and was implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. Safety assessment included adverse events (AEs), vital signs, 12-lead ECG parameters, clinical laboratory, immunogenicity, physical examination and other parameters considered relevant for the safety assessments.

Background therapy:

Methotrexate and folic acid

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 14 December 2010 |
| 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 | Romania: 23 |
| Country: Number of subjects enrolled | Turkey: 7 |
| Country: Number of subjects enrolled | India: 24 |
| Country: Number of subjects enrolled | Argentina: 20 |
| Country: Number of subjects enrolled | Brazil: 50 |
| Country: Number of subjects enrolled | Russian Federation: 17 |
| Country: Number of subjects enrolled | United States: 29 |
| Country: Number of subjects enrolled | Spain: 33 |
| Country: Number of subjects enrolled | Austria: 20 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Estonia: 2 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Hungary: 4 |

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 11 |
| Worldwide total number of subjects | 312 |
| EEA total number of subjects | 165 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 246 |
| From 65 to 84 years | 66 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in two parts with similar study designs. In Study Part I patients were randomized to either GP2013 or MabThera. In Study Part II patients were randomized to either GP2013 or Rituxan.

Pre-assignment

Screening details:

An optional anti-TNF or DMARD (except MTX, sulfasalazine, chloroquine, and hydrochloroquine) washout period could be performed between Visit 1- Screening and Visit 2 -Baseline. At Visit 2 the RA status and associated laboratory testing was reassessed in order to confirm eligibility of the patient. Visit 3- Randomization was within 7 days \pm 2 days.

Period 1

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

Blinding implementation details:

Patients, investigators, assessors, and blinded staff of the CRO remained blinded to the identity of the treatment from the time of randomization until database lock. Investigational product was packed in an open label design. Receipt, storage and preparation of the medication were performed by unblinded site staff only. They ensured that no other persons than unblinded staff members (site and CRO) had access to the medication and the documentation of study medication.

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | No |
| Arm title | GP2013 (pooled) |

Arm description:

This treatment arm includes all patients, randomized to GP2013 in both Study Part I and Study Part II.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GP2013 |
| Investigational medicinal product code | rituximab |
| Other name | Sandoz biosimilar rituximab |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

10 mg/mL in 500 mg (50 mL) single-use vials. For i.v. administration, two 500 mg vials (1000 mg of active molecule) of concentrate are diluted in 0.9% NaCl solution and infused i.v. The treatment course consists of 2 i.v. infusions 2 weeks apart (at Day 1 and Day 15)

| | |
|------------------|----------|
| Arm title | Rituxan® |
|------------------|----------|

Arm description:

This treatment arm includes patients, randomized to Rituxan® in the Study Part II

| | |
|--|------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituxan® |
| Investigational medicinal product code | rituximab |
| Other name | rituximab-US |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

10 mg/mL in 500 mg (50 mL) single-use vials. For i.v. administration, two 500 mg vials (1000 mg of active molecule) of concentrate are diluted in 0.9% NaCl solution and infused i.v. The treatment course

consists of 2 i.v. infusions 2 weeks apart (at Day 1 and Day 15)

| | |
|---|------------------------------------|
| Arm title | MabThera® |
| Arm description: This treatment arm includes patients, randomized to MabThera® in the Study Part I | |
| Arm type | Active comparator |
| Investigational medicinal product name | MabThera® |
| Investigational medicinal product code | rituximab |
| Other name | rituximab-EU |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

10 mg/mL in 500 mg (50 mL) single-use vials. For i.v. administration, two 500 mg vials (1000 mg of active molecule) of concentrate are diluted in 0.9% NaCl solution and infused i.v. The treatment course consists of 2 i.v. infusions 2 weeks apart (at Day 1 and Day 15)

| | |
|--|------------------------------------|
| Arm title | GP2013 (Part I) |
| Arm description: This treatment arm includes patents randomized to GP2013 in Study Part I only. Patients from this treatment arm are also included in the treatment arm GP2013 (pooled). This treatment arm is used for some of efficacy comparisons (secondary endpoints), which were done on the result of the Study Part I only. | |
| Arm type | Experimental |
| Investigational medicinal product name | GP2013 |
| Investigational medicinal product code | rituximab |
| Other name | Sandoz biosimilar rituximab |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

10 mg/mL in 500 mg (50 mL) single-use vials. For i.v. administration, two 500 mg vials (1000 mg of active molecule) of concentrate are diluted in 0.9% NaCl solution and infused i.v. The treatment course consists of 2 i.v. infusions 2 weeks apart (at Day 1 and Day 15)

| Number of subjects in period 1 | GP2013 (pooled) | Rituxan® | MabThera® |
|---------------------------------------|-----------------|----------|-----------|
| Started | 133 | 92 | 87 |
| 24 weeks | 123 | 84 | 83 |
| Completed | 112 | 80 | 69 |
| Not completed | 21 | 12 | 18 |
| Adverse event, serious fatal | 1 | 1 | - |
| Consent withdrawn by subject | 5 | 3 | 5 |
| Adverse event, non-fatal | 4 | 3 | 5 |
| Lost to follow-up | 2 | 1 | 3 |
| Lack of efficacy | 6 | 4 | 3 |
| Protocol deviation | 3 | - | 2 |

| Number of subjects in period 1 | GP2013 (Part I) |
|---------------------------------------|-----------------|
| Started | 86 |
| 24 weeks | 79 |
| Completed | 73 |
| Not completed | 13 |
| Adverse event, serious fatal | 1 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 3 |
| Lost to follow-up | 1 |
| Lack of efficacy | 5 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------|
| Reporting group title | GP2013 (pooled) |
| Reporting group description: | |
| This treatment arm includes all patients, randomized to GP2013 in both Study Part I and Study Part II. | |
| Reporting group title | Rituxan® |
| Reporting group description: | |
| This treatment arm includes patients, randomized to Rituxan® in the Study Part II | |
| Reporting group title | MabThera® |
| Reporting group description: | |
| This treatment arm includes patients, randomized to MabThera® in the Study Part I | |
| Reporting group title | GP2013 (Part I) |
| Reporting group description: | |
| This treatment arm includes patients randomized to GP2013 in Study Part I only. Patients from this treatment arm are also included in the treatment arm GP2013 (pooled). This treatment arm is used for some of efficacy comparisons (secondary endpoints), which were done on the result of the Study Part I only. | |

| Reporting group values | GP2013 (pooled) | Rituxan® | MabThera® |
|--|-----------------|----------|-----------|
| Number of subjects | 133 | 92 | 87 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.42 | 54.95 | 52.17 |
| standard deviation | ± 11.779 | ± 10.750 | ± 12.531 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 111 | 78 | 73 |
| Male | 22 | 14 | 14 |
| Number of prior anti-TNFs | | | |
| Units: Subjects | | | |
| One | 109 | 73 | 70 |
| Two | 18 | 13 | 16 |
| More than two | 6 | 6 | 1 |
| Anti-drug antibodies (ADA) | | | |
| Units: Subjects | | | |
| Negative | 132 | 87 | 85 |

| | | | |
|----------|---|---|---|
| Positive | 0 | 3 | 2 |
| Missing | 1 | 2 | 0 |

| | | | |
|---|---------|---------|---------|
| BMI | | | |
| Analysis was performed on data of BMI available at the baseline visit: GP2013 (pooled) - 133 patients; Rituxan - 92 patients; MabThera - 85 patients; GP2013 part I - 86 patients. | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 27.37 | 29.66 | 27.25 |
| standard deviation | ± 6.230 | ± 6.606 | ± 6.000 |
| Duration of RA | | | |
| Analysis was done on data of Duration of RA available at the baseline visit: GP2013 (pooled) - 133 patients; Rituxan - 92 patients; MabThera - 86 Patients; GP2013 Part I - 86 patients. | | | |
| Units: years | | | |
| arithmetic mean | 10.53 | 11.10 | 10.81 |
| standard deviation | ± 8.074 | ± 8.299 | ± 7.137 |
| DAS28-CRP | | | |
| Analysis was done on data of DAS28-CRP, available at the baseline visit: GP2013 (pooled) - 132 patients; Rituxan - 91 patients; MabThera - 87 patients; GP2013 Part I - 85 patients. | | | |
| Units: units | | | |
| arithmetic mean | 5.83 | 5.91 | 5.85 |
| standard deviation | ± 0.922 | ± 1.009 | ± 0.880 |
| Dose of methotrexate at baseline | | | |
| Analysis was done on data of Dose of methotrexate, available at the baseline visit: GP2013 (pooled) - 131 patients; Rituxan - 91 patients; MabThera - 84 patients; GP2013 Part I - 84 patients. | | | |
| Units: mg/week | | | |
| arithmetic mean | 15.09 | 15.29 | 14.65 |
| standard deviation | ± 4.856 | ± 4.888 | ± 5.154 |

| Reporting group values | GP2013 (Part I) | Total | |
|--|-----------------|-------|--|
| Number of subjects | 86 | 312 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.72 | | |
| standard deviation | ± 12.135 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 76 | 262 | |
| Male | 10 | 50 | |

| | | | |
|---|---------|-----|--|
| Number of prior anti-TNFs | | | |
| Units: Subjects | | | |
| One | 72 | 252 | |
| Two | 10 | 47 | |
| More than two | 4 | 13 | |
| Anti-drug antibodies (ADA) | | | |
| Units: Subjects | | | |
| Negative | 85 | 304 | |
| Positive | 0 | 5 | |
| Missing | 1 | 3 | |
| BMI | | | |
| Analysis was performed on data of BMI available at the baseline visit: GP2013 (pooled) - 133 patients; Rituxan - 92 patients; MabThera - 85 patients; GP2013 part I - 86 patients. | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 27.20 | | |
| standard deviation | ± 6.121 | - | |
| Duration of RA | | | |
| Analysis was done on data of Duration of RA available at the baseline visit: GP2013 (pooled) - 133 patients; Rituxan - 92 patients; MabThera - 86 Patients; GP2013 Part I - 86 patients. | | | |
| Units: years | | | |
| arithmetic mean | 9.34 | | |
| standard deviation | ± 6.818 | - | |
| DAS28-CRP | | | |
| Analysis was done on data of DAS28-CRP, available at the baseline visit: GP2013 (pooled) - 132 patients; Rituxan - 91 patients; MabThera - 87 patients; GP2013 Part I - 85 patients. | | | |
| Units: units | | | |
| arithmetic mean | 5.81 | | |
| standard deviation | ± 0.916 | - | |
| Dose of methotrexate at baseline | | | |
| Analysis was done on data of Dose of methotrexate, available at the baseline visit: GP2013 (pooled) - 131 patients; Rituxan - 91 patients; MabThera - 84 patients; GP2013 Part I - 84 patients. | | | |
| Units: mg/week | | | |
| arithmetic mean | 14.59 | | |
| standard deviation | ± 4.618 | - | |

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | GP2013 (pooled) |
| Reporting group description: This treatment arm includes all patients, randomized to GP2013 in both Study Part I and Study Part II. | |
| Reporting group title | Rituxan® |
| Reporting group description: This treatment arm includes patients, randomized to Rituxan® in the Study Part II | |
| Reporting group title | MabThera® |
| Reporting group description: This treatment arm includes patients, randomized to MabThera® in the Study Part I | |
| Reporting group title | GP2013 (Part I) |
| Reporting group description: This treatment arm includes patients randomized to GP2013 in Study Part I only. Patients from this treatment arm are also included in the treatment arm GP2013 (pooled). This treatment arm is used for some of efficacy comparisons (secondary endpoints), which were done on the result of the Study Part I only. | |

Primary: Pharmacokinetics (PK): AUC(0-inf) in serum samples, collected over 24 weeks

| | |
|--|--|
| End point title | Pharmacokinetics (PK): AUC(0-inf) in serum samples, collected over 24 weeks ^[1] |
| End point description: PK bioequivalence is defined as AUC(0-inf) of the drugs being comparable, i.e. the two-sided 90% CI for the ratio of the geometric means (GP2013/MabThera) is within the predefined bioequivalence limits of 0.8 to 1.25. The PK parameters were transformed prior to analysis using a logarithmic transformation. An analysis of variance (ANOVA) was used to analyze the transformed data including treatment group only as a factor in the model. The confidence interval for the difference between the two products on the transformed scale was obtained from the ANOVA model, which was then be back-transformed (exp base e) to obtain the confidence interval for the ratio on the original scale. | |
| End point type | Primary |
| End point timeframe: 24 weeks | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: 3-way equivalence testing, comparing entire GP2013 cohort (GP2013 pooled treatment arm); MabThera treatment arm and Rituxan treatment arm was performed. Results of comparison of GP2013 Part I, being a subpopulation of the GP2013 cohort, are not provided.

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | |
|---|--------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 124 ^[2] | 80 ^[3] | 79 ^[4] | |
| Units: units on a scale | | | | |
| geometric mean (geometric coefficient of variation) | 7627.44 (± 38.60) | 7536.89 (± 40.28) | 6896.97 (± 40.56) | |

Notes:

[2] - PK analysis set

[3] - PK analysis set

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Bioequivalence GP2013 vs MabThera |
| Comparison groups | GP2013 (pooled) v MabThera® |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[5] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.106 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 1.21 |

Notes:

[5] - GP2013 arm is the numerator and MabThera arm is the denominator for the geometric mean ratio

| | |
|---|----------------------------------|
| Statistical analysis title | Bioequivalence GP2013 vs Rituxan |
| Comparison groups | GP2013 (pooled) v Rituxan® |
| Number of subjects included in analysis | 204 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[6] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.012 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.925 |
| upper limit | 1.108 |

Notes:

[6] - GP2013 arm is the numerator and Rituxan arm is the denominator for the geometric mean ratio.

| | |
|---|---------------------------------------|
| Statistical analysis title | Bioequivalence of Rituxan vs MabThera |
| Comparison groups | Rituxan® v MabThera® |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[7] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.093 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.989 |
| upper limit | 1.208 |

Notes:

[7] - Rituxan arm is the numerator and MabThera arm is the denominator for the geometric mean ratio.

Secondary: Pharmacokinetics (PK): Cmax after first infusion (Cmax1)

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK): Cmax after first infusion (Cmax1) ^[8] |
|-----------------|---|

End point description:

A key secondary PK endpoint was the maximum serum concentration after the first infusion (Cmax1). In order to claim bioequivalence, the 90% CI must be entirely within the standard equivalence limits of 0.8-1.25.

The PK parameters were transformed prior to analysis using a logarithmic transformation. An analysis of variance (ANOVA) was used to analyze the transformed data including treatment group only as a factor in the model. The confidence interval for the difference between the two products on the transformed scale was obtained from the ANOVA model, which was then be back-transformed (exp base e) to obtain the confidence interval for the ratio on the original scale.

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

End point timeframe:

not applicable

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: 3-way equivalence testing, comparing entire GP2013 cohort (GP2013 pooled treatment arm); MabThera treatment arm and Rituxan treatment arm was performed. Results of comparison of GP2013 Part I, being a subpopulation of the GP2013 cohort, are not provided.

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | |
|---|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 120 ^[9] | 82 ^[10] | 78 ^[11] | |
| Units: unit(s) | | | | |
| geometric mean (geometric coefficient of variation) | 361.53 (± 40.82) | 335.88 (± 42.65) | 319.80 (± 42.75) | |

Notes:

[9] - PK-Analysis set, patients with available data

[10] - PK-analysis set, patients with available data

[11] - PK-analysis set, patients with available data

Statistical analyses

| Statistical analysis title | Bioequivalence GP2013 vs MabThera |
|---|-----------------------------------|
| Comparison groups | GP2013 (pooled) v MabThera® |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[12] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.131 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.027 |
| upper limit | 1.244 |

Notes:

[12] - GP2013 arm is the numerator and MabThera arm is the denominator for the geometric mean ratio.

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | Bioequivalence of GP2013 vs Rituxan |
|----------------------------|-------------------------------------|

| | |
|---|-----------------------------|
| Comparison groups | GP2013 (pooled) v Rituxan® |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[13] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.076 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.979 |
| upper limit | 1.184 |

Notes:

[13] - GP2013 arm is the numerator and Rituxan arm is the denominator for the geometric mean ratio.

| | |
|---|---------------------------------------|
| Statistical analysis title | Bioequivalence of Rituxan vs MabThera |
| Comparison groups | Rituxan® v MabThera® |
| Number of subjects included in analysis | 160 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[14] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.946 |
| upper limit | 1.167 |

Notes:

[14] - Rituxan arm is the numerator and MabThera arm is the denominator for the geometric mean ratio.

Secondary: Pharmacodynamics (PD): AUEC(0-14d) of percent B-cells relative to baseline

| | |
|-----------------|--|
| End point title | Pharmacodynamics (PD): AUEC(0-14d) of percent B-cells relative to baseline ^[15] |
|-----------------|--|

End point description:

The key secondary PD endpoint was depletion of peripheral B-cells, defined as the area under the effect time curves (AUEC) of the percent change of blood CD20+ B-cell count relative to baseline, up to Day 15 (i.e., up to the second infusion).

To conclude equivalence the 95% CI must be entirely within the standard equivalence limits of 0.8-1.25

Ratio of geometric means and 95% confidence interval were estimated by an analysis of variance (ANOVA) on log-transformed PD parameter with treatment as the factor. Results were then back-transformed to the original scale.

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

End point timeframe:

14 days

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: 3-way equivalence testing, comparing entire GP2013 cohort (GP2013 pooled treatment arm); MabThera treatment arm and Rituxan treatment arm was performed. Results of comparison of GP2013 Part I, being a subpopulation of the GP2013 cohort, are not provided.

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | |
|---|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 110 ^[16] | 80 ^[17] | 76 ^[18] | |
| Units: unit(s) | | | | |
| geometric mean (geometric coefficient of variation) | 1226.53 (\pm 2.83) | 1240.57 (\pm 1.95) | 1201.15 (\pm 8.91) | |

Notes:

[16] - PK analysis set, patients with available data

[17] - PK analysis set, patients with available data

[18] - PK analysis set, patients with available data

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | PD equivalence GP2013 vs Rituxan |
| Comparison groups | GP2013 (pooled) v Rituxan® |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[19] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.989 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.974 |
| upper limit | 1.004 |

Notes:

[19] - GP2013 arm is the numerator and Rituxan arm is the denominator for the geometric mean ratio.

| | |
|---|------------------------------------|
| Statistical analysis title | PD equivalence GP2013 vs. MabThera |
| Comparison groups | GP2013 (pooled) v MabThera® |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[20] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.021 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.003 |
| upper limit | 1.04 |

Notes:

[20] - GP2013 arm is the numerator and MabThera arm is the denominator for the geometric mean ratio.

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | PD equivalence Rituxan vs MabThera |
| Comparison groups | Rituxan® v MabThera® |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[21] |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.033 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.016 |
| upper limit | 1.05 |

Notes:

[21] - Rituxan arm is the numerator and MabThera arm is the denominator for the geometric mean ratio.

Secondary: Efficacy: Change from baseline in DAS28 (CRP) at Week 24

| | |
|-----------------|--|
| End point title | Efficacy: Change from baseline in DAS28 (CRP) at Week 24 |
|-----------------|--|

End point description:

The key secondary efficacy endpoint was change from baseline in DAS28 (CRP) at Week 24. This efficacy endpoint was analyzed using the PP analysis set as it constitutes the most conservative approach for non-inferiority evaluation. Non-inferiority was to be concluded if the upper limit of the 95% CI for the mean difference between GP2013 and MabThera® or GP2013 and Rituxan® was less than or equal to the non-inferiority margin of 0.6.

This margin was statistically justified by the results of the REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) trial (Cohen et al 2006) providing a 95% CI for the mean difference between rituximab/MTX and MTX alone of (-1.74;-1.25). The margin of 0.6 was determined by retaining more than 50% of the reference treatment effect which was considered clinically acceptable. The non-inferiority margin is further justified by the EULAR criteria which define "no response" as change from baseline being < 0.6.

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

End point timeframe:

24 weeks

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | GP2013 (Part I) |
|-------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 128 ^[22] | 85 ^[23] | 82 ^[24] | 85 ^[25] |
| Units: unit(s) | | | | |
| least squares mean (standard error) | -2.07 (± 0.103) | -1.99 (± 0.126) | -2.23 (± 0.143) | -2.16 (± 0.142) |

Notes:

[22] - PP analysis set, patients with available data

[23] - PP analysis set, patients with available data

[24] - PP analysis set, patients with available data

[25] - PP analysis set, patients with available data

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | Non-Inferiority of GP2013 vs Rituxan |
|----------------------------|--------------------------------------|

Statistical analysis description:

LS means, standard errors and 95% CI were estimated by a repeated measures mixed model with treatment, time and treatment*time interaction term as categorical variables and baseline DAS28 as a continuous variable.

A negative change from baseline represents an improvement in assessment of rheumatoid arthritis.

| | |
|---|---------------------------------|
| Comparison groups | GP2013 (pooled) v Rituxan® |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[26] |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.397 |
| upper limit | 0.24 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.162 |

Notes:

[26] - The direction of comparison is LS mean of GP2013 - LS mean of Rituxan

| | |
|-----------------------------------|--|
| Statistical analysis title | Non-Inferiority of GP2013 vs. MabThera |
|-----------------------------------|--|

Statistical analysis description:

LS means, standard errors and 95% CI were estimated by a repeated measures mixed model with treatment, time and treatment*time interaction term as categorical variables and baseline DAS28 as a continuous variable.

A negative change from baseline represents an improvement in assessment of rheumatoid arthritis.

| | |
|---|---------------------------------|
| Comparison groups | MabThera® v GP2013 (Part I) |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[27] |
| Parameter estimate | LS Mean difference |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.328 |
| upper limit | 0.462 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.201 |

Notes:

[27] - The direction of comparison is LS mean of GP2013 Part I - LS mean of MabThera

Secondary: Efficacy: ACR20 (CRP) response at Week 24

| | |
|---|---|
| End point title | Efficacy: ACR20 (CRP) response at Week 24 |
| End point description: | |
| A two-sided 95% CI for the difference in the ACR20 (CRP) response rates at Week 24 was estimated. The lower bound of the CI was compared to a margin of -15.0% and had to be greater than -15.0% to conclude non-inferiority. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 weeks | |

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | GP2013 (Part I) |
|---|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 119 ^[28] | 80 ^[29] | 76 ^[30] | 78 ^[31] |
| Units: Number of patients with ACR20 response | 86 | 50 | 55 | 56 |

Notes:

[28] - PP analysis set, patients with available data

[29] - PP analysis set, patients with available data

[30] - PP analysis set, patients with available data

[31] - PP analysis set, patients with available data

Statistical analyses

| Statistical analysis title | Non-Inferiority of GP2013 vs. Rituxan |
|----------------------------|---------------------------------------|
|----------------------------|---------------------------------------|

Statistical analysis description:

To conclude non-inferiority the lower 95% CI should be greater than -15.0%.

The predefined noninferiority margin of 0.15 for ACR20 is based on the historical placebo-controlled phase III study to evaluate the response rate benefit of adding rituximab to the conventional small molecule-based treatment of patients with RA (Cohen et al. 2006).

| | |
|---|---------------------------------|
| Comparison groups | GP2013 (pooled) v Rituxan® |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[32] |
| Parameter estimate | Response rate difference |
| Point estimate | 9.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.54 |
| upper limit | 23.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.79 |

Notes:

[32] - The direction of comparison is response rate of GP2013 - response rate of Rituxan

| Statistical analysis title | Non-Inferiority of GP2013 vs. MabThera |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

To conclude non-inferiority the lower 95% CI should be greater than -15.0%.

The predefined noninferiority margin of 0.15 for ACR20 is based on the historical placebo-controlled phase III study to evaluate the response rate benefit of adding rituximab to the conventional small molecule-based treatment of patients with RA (Cohen et al. 2006).

| | |
|---|---------------------------------|
| Comparison groups | MabThera® v GP2013 (Part I) |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[33] |
| Parameter estimate | Response rate difference |
| Point estimate | -0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.74 |
| upper limit | 13.6 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.23 |

Notes:

[33] - The direction of comparison is response rate of GP2013 Part I - response rate of MabThera

Secondary: Efficacy: Summary of disease activity according to CDAI

| | |
|---|---|
| End point title | Efficacy: Summary of disease activity according to CDAI |
| End point description: A proportion of patients with different levels of RA disease activity according to CDAI at study week 24 is presented | |
| End point type | Secondary |
| End point timeframe: 24 weeks | |

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | GP2013 (Part I) |
|-----------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 119 ^[34] | 80 ^[35] | 75 ^[36] | 78 ^[37] |
| Units: Patients | | | | |
| High disease activity | 26 | 20 | 18 | 18 |
| Moderate disease activity | 45 | 32 | 26 | 24 |
| Low disease activity | 41 | 25 | 19 | 30 |
| Remission | 7 | 3 | 12 | 6 |

Notes:

[34] - PP analysis set, patients with available data

[35] - PP analysis set, patients with available data

[36] - PP analysis set, patients with available data

[37] - PP analysis set, patients with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Summary of disease activity according to SDAI

| | |
|---|---|
| End point title | Efficacy: Summary of disease activity according to SDAI |
| End point description: A proportion of patients with different levels of RA disease activity according to SDAI at study week 24 is presented | |
| End point type | Secondary |
| End point timeframe: 24 weeks | |

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | GP2013 (Part I) |
|-----------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 117 ^[38] | 77 ^[39] | 74 ^[40] | 77 ^[41] |
| Units: Patients | | | | |
| High disease activity | 20 | 15 | 15 | 13 |
| Moderate disease activity | 48 | 34 | 29 | 27 |
| Low disease activity | 41 | 26 | 18 | 31 |
| Remission | 8 | 2 | 12 | 6 |

Notes:

[38] - PP analysis set - patients with available values

[39] - PP analysis set - patients with available values

[40] - PP analysis set - patients with available values

[41] - PP analysis set - patients with available values

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: EULAR response at week 24

| | |
|------------------------|-------------------------------------|
| End point title | Efficacy: EULAR response at week 24 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 24 weeks | |

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | GP2013 (Part I) |
|-----------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 116 ^[42] | 77 ^[43] | 75 ^[44] | 76 ^[45] |
| Units: Patients | | | | |
| Good response | 0 | 0 | 0 | 0 |
| Moderate response | 101 | 61 | 63 | 67 |
| No response | 15 | 16 | 12 | 9 |

Notes:

[42] - PP analysis set, patients with available data

[43] - PP analysis set, patients with available data

[44] - PP analysis set, patients with available data

[45] - PP analysis set, patients with available data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunogenicity (ADA Formation)

| | |
|--|--|
| End point title | Immunogenicity (ADA Formation) ^[46] |
| End point description: | |
| For patients, who received a second optional treatment course, which could be given at any time between week 24 and week 52 an additional follow-up period of 26 weeks after the first infusion of the | |

second treatment course was required. Immunogenicity was also assessed in that 26 weeks follow up study visit.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Entire study duration, which means at least 52 weeks for patients who completed the study.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data of immunogenicity is provided for GP2013 pooled treatment arm, it includes immunogenicity data of the GP2013 Part I patients. For this no data are separately provided for GP2013 Part I.

| End point values | GP2013 (pooled) | Rituxan® | MabThera® | |
|---|---------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 127 ^[47] | 82 ^[48] | 84 ^[49] | |
| Units: Patients with at least 1 ADA+ sample | 21 | 11 | 18 | |

Notes:

[47] - Safety analysis set, patients with negative ADA results at randomization and available data

[48] - Safety analysis set, patients with negative ADA results at randomization and available data

[49] - Safety analysis set, patients with negative ADA results at randomization and available data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire study duration, which means at least 52 weeks for patients who completed the study.

Adverse event reporting additional description:

For patients, who received a second optional treatment course, which could be given at any time between week 24 and week 52 an additional follow-up period of 26 weeks after the first infusion of the second treatment course was required. These patients had respectively longer study duration of maximally 1.5 years.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | GP2013 (pooled) |
|-----------------------|-----------------|

Reporting group description:

This treatment arm includes all patients, randomized to GP2013 in both Study Part I and Study Part II.

| | |
|-----------------------|----------|
| Reporting group title | Rituxan® |
|-----------------------|----------|

Reporting group description:

This treatment arm includes patients, randomized to Rituxan® in the Study Part II

| | |
|-----------------------|-----------|
| Reporting group title | MabThera® |
|-----------------------|-----------|

Reporting group description:

This treatment arm includes patients, randomized to MabThera® in the Study Part I

| Serious adverse events | GP2013 (pooled) | Rituxan® | MabThera® |
|---|-------------------|----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 133 (12.03%) | 9 / 92 (9.78%) | 14 / 87 (16.09%) |
| number of deaths (all causes) | 1 | 1 | 0 |
| number of deaths resulting from adverse events | 1 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Vascular disorders | | | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |

| | | | |
|--|--|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Lipogranuloma | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Urogenital prolapse | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Dissociative disorder | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 2 / 92 (2.17%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 2 / 92 (2.17%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone fissure | Additional description: SAEs: bone fissure, Vitamid D defficiency and fractured sacrum occurred in same patient as a sequence of events | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |

| | | | |
|---|--|----------------|----------------|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fractured sacrum | Additional description: SAEs: bone fissure, Vitamid D deficiency and fractured sacrum occurred in same patient as a sequence of events | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Overdose | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial rupture | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |

| | | | |
|---|--|----------------|----------------|
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Sinus tachycardia | Additional description: SAEs chest pain and sinus tachycardia were diagnosed in same patient at the same time. | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningoradiculitis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |

| | | | |
|---|--|----------------|----------------|
| Bone marrow failure | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 | | | |
| Fistula | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 0 / 92 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Fracture pain | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Rheumatoid arthritis | | | |

| | | | |
|---|--|----------------|----------------|
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin abscess | Additional description: SAEs Fistula, Groin Abscess and Pilonidal cyst occurred in same patient as a sequence of events. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Lyme disease | | | |

| | | | |
|---|--|----------------|----------------|
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Pilonidal cyst | Additional description: SAEs Fistula, Groin Abscess and Pilonidal cyst occurred in same patient as a sequence of events | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Purulent pericarditis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 0 / 92 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | Additional description: SAEs: Bone marrow failure, Pancytopenia, Sepsis, Septic shock, Multiple organ dysfunction syndrome and Overdose occurred in same patient as a sequence of events due to Methotrexate overdose. | | |
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Soft tissue infection | | | |

| | | | |
|---|--|----------------|----------------|
| subjects affected / exposed | 1 / 133 (0.75%) | 0 / 92 (0.00%) | 0 / 87 (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 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | Additional description: SAEs: bone fissure, Vitamid D deficiency and fractured sacrum occurred in same patient as a sequence of events | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | GP2013 (pooled) | Rituxan® | MabThera® |
|---|-------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 87 / 133 (65.41%) | 60 / 92 (65.22%) | 56 / 87 (64.37%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 3 / 92 (3.26%) | 5 / 87 (5.75%) |
| occurrences (all) | 5 | 3 | 8 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 1 / 92 (1.09%) | 0 / 87 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 1 / 92 (1.09%) | 3 / 87 (3.45%) |
| occurrences (all) | 3 | 1 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 7 / 92 (7.61%) | 4 / 87 (4.60%) |
| occurrences (all) | 5 | 7 | 4 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 3 / 92 (3.26%) | 2 / 87 (2.30%) |
| occurrences (all) | 0 | 4 | 2 |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|--|--|---|--|
| subjects affected / exposed occurrences (all) | 0 / 133 (0.00%) 0 | 3 / 92 (3.26%) 3 | 0 / 87 (0.00%) 0 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 133 (2.26%) 4 | 3 / 92 (3.26%) 4 | 1 / 87 (1.15%) 1 |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 4 / 133 (3.01%) 4 | 2 / 92 (2.17%) 2 | 3 / 87 (3.45%) 6 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 6 / 133 (4.51%) 6 | 6 / 92 (6.52%) 10 | 5 / 87 (5.75%) 7 |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) | 1 / 133 (0.75%) 1 | 3 / 92 (3.26%) 3 | 1 / 87 (1.15%) 1 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) | 9 / 133 (6.77%) 9 4 / 133 (3.01%) 4 | 5 / 92 (5.43%) 10 1 / 92 (1.09%) 1 | 3 / 87 (3.45%) 3 3 / 87 (3.45%) 3 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 5 / 133 (3.76%) 5 2 / 133 (1.50%) 3 | 1 / 92 (1.09%) 1 1 / 92 (1.09%) 2 | 4 / 87 (4.60%) 5 6 / 87 (6.90%) 6 |
| Musculoskeletal and connective tissue disorders Rheumatoid arthritis subjects affected / exposed occurrences (all) Back pain | 6 / 133 (4.51%) 6 | 8 / 92 (8.70%) 14 | 5 / 87 (5.75%) 5 |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 4 / 133 (3.01%) 4 | 3 / 92 (3.26%) 3 | 4 / 87 (4.60%) 5 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 133 (6.77%) | 9 / 92 (9.78%) | 5 / 87 (5.75%) |
| occurrences (all) | 12 | 11 | 6 |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 133 (8.27%) | 2 / 92 (2.17%) | 5 / 87 (5.75%) |
| occurrences (all) | 12 | 2 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 133 (4.51%) | 6 / 92 (6.52%) | 5 / 87 (5.75%) |
| occurrences (all) | 7 | 6 | 5 |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 1 / 92 (1.09%) | 5 / 87 (5.75%) |
| occurrences (all) | 6 | 1 | 6 |
| Oral herpes | | | |
| subjects affected / exposed | 5 / 133 (3.76%) | 1 / 92 (1.09%) | 2 / 87 (2.30%) |
| occurrences (all) | 6 | 1 | 2 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 5 / 92 (5.43%) | 1 / 87 (1.15%) |
| occurrences (all) | 0 | 5 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 133 (0.00%) | 1 / 92 (1.09%) | 3 / 87 (3.45%) |
| occurrences (all) | 0 | 1 | 4 |
| Metabolism and nutrition disorders | | | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 2 / 133 (1.50%) | 5 / 92 (5.43%) | 2 / 87 (2.30%) |
| occurrences (all) | 3 | 5 | 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 04 March 2011 | <p>The co-primary endpoints (AUC0-inf and Cmax) were changed to one single primary endpoint (AUC0-inf) and a key secondary endpoint (Cmax). Changing infusion rates due to long time of rituximab infusions in accordance with SmPC were expected to cause larger variability for Cmax than for AUC0-inf and therefore AUC0-inf was considered a more reliable parameter for the PK comparability. The CI was changed from 90% to 95% CI for the PD endpoints according to the "Guideline on the Choice of the Non-Inferiority margin" (EMA/CPMP/EWP/2158/99).</p> <p>In the original protocol, patients were requested to take a short course of oral corticosteroids (60 mg/day on Days 2-7 and 30 mg/day on Days 8-14). Amendment 1 eliminated this to reflect the recommendations of the current MabThera SmPC.</p> |
| 04 April 2011 | <p>A mandatory HIV test was added at Screening as per request of the Argentinean Health Authority. This change was applicable in Argentina only.</p> |
| 21 November 2011 | <p>The inclusion/exclusion criteria were amended to reflect more current practice since the time the REFLEX trial was conducted</p> |
| 06 March 2013 | <p>Introduced a third treatment arm Rituxan (reference rituximab licensed in the USA) to be compared to both GP2013 and MabThera (EU) aiming the clinical bridge between MabThera and Rituxan.</p> <p>The mean change from Baseline in DAS28 at Week 24 was made a key secondary endpoint. A supportive analysis of ACR20, similar to that of DAS28, was added.</p> |
| 30 October 2013 | <p>was implemented following a Drug Safety Communication from the US Health Authority (Food and Drug Administration; FDA) on 25-Sep-2013 announcing the addition of a Boxed Warning to Rituxan prescribing information concerning the potential for hepatitis B virus (HBV) reactivation.</p> |
| 23 June 2014 | <p>Gender was removed as a covariate from all PK analyses performed in Study Part II following discussions with the US FDA.</p> <p>Specifically mentioned "MabThera" or "Rituxan" instead of the general term "reference product" in order to clearly distinguish between EU-approved rituximab (MabThera), used as comparator in part I of the study, and US-licensed rituximab (Rituxan), used as comparator in Study Part II.</p> |
| 04 August 2014 | <p>The wording and use of terms were adapted to implement FDA's advice for clear distinction between the terms and underlying concepts of "comparability" and "similarity".</p> |
| 09 June 2015 | <p>Safety precautions, in accordance with the MTX label, in relation to contraception requirements to prevent fathering a child or becoming pregnant were included. As per request of the Polish Health Authority, the time frame in which a highly effective method of birth control, required for women of child bearing potential treated with rituximab, is specified to be consistent with the requirements currently in the Informed Consent Form.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28637670>