



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
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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	Investigator, Monitor, Data analyst, Carer, Subject, 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®
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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]
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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
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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
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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]
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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
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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 (± 2.83)	1240.57 (± 1.95)	1201.15 (± 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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	GP2013 (pooled)
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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®
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Reporting group description:

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

Reporting group title	MabThera®
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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>