Clinical trial results:
A randomized, double- blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to GP2013 or re-treatment with Rituxan® or MabThera® in patients with active rheumatoid arthritis, previously treated with Rituxan® or MabThera®

Summary

EudraCT number	2012-003876-38
Trial protocol	DE HU PL
Global end of trial date	12 October 2016

Results information

Result version number	v1 (current)
This version publication date	27 October 2017
First version publication date	27 October 2017

Trial information

Trial identification

Sponsor protocol code	GP13-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02514772
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, +49 80244760, biopharma.clinicaltrials@sandoz.com
Scientific contact	Strategic Planning Biopharma Clinical Development, Sandoz, +49 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	12 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2016
Global end of trial reached?	Yes
Global end of trial date	12 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective is to identify potential safety risk of the transition from the originator product (US-licensed Rituxan® or EU-approved MabThera®) to GP2013 (proposed biosimilar product) as compared to continuous treatment with the originator product in terms of general safety and immunogenicity.

Protection of trial subjects:

This trial was designed, conducted and reported in accordance with the international Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), applicable local regulations (including European Directive 2001/20/EC), and following the ethical principles laid down in the Declaration of Helsinki. Specific ICH adopted and other relevant international guidelines and recommendations were taken into account as far as meaningfully possible. Safety assessments included adverse events (AEs), vital signs, 12-lead ECG parameters, clinical laboratory, immunogenicity, physical examination and other parameters considered relevant for the safety assessment, of Rituximab.

Background therapy:

Metothrexate and Folic Acid

Evidence for comparator: -

Actual start date of recruitment	15 June 2015
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	Poland: 11
Country: Number of subjects enrolled	Germany: 50
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	107
EEA total number of subjects	72

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)	83
From 65 to 84 years	23
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 194 patients were screened at 54 centers in 4 countries, i.e. USA, Germany, Hungary, and Poland. Of these, 107 patients were randomized to either GP2013 (53 patients) or Rituxan/MabThera (54 patients).

Pre-assignment

Screening details:

In the screening period of 4 weeks patients' eligibility and status regarding positivity of anti-drug-antibodies (ADA; since study patients had already been treated previously with either commercial Rituxan® or MabThera® were tested.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	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?	Yes
Arm title	GP2013

Arm description:

Patients in this group were switched from originator rituximab (which they received before study participation) to GP2013 - biosimilar rituximab

Arm type	Experimental
Investigational medicinal product name	GP2013
Investigational medicinal product code	rituximab
Other name	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 14)

Arm title	Rituxan®/MabThera®

Arm description:

Patients in this group received same originator rituximab version as they had received before study participation.

Arm type	Active comparator
Investigational medicinal product name	Rituxan®/MabThera®
Investigational medicinal product code	rituximab
Other name	
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 14)

Number of subjects in period 1	GP2013	Rituxan®/MabThera®
Started	53	54
Completed	50	52
Not completed	3	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	GP2013
Reporting group description:	
Patients in this group were switched from originator rituximab (which they received before study participation) to GP2013 - biosimilar rituximab	
Reporting group title	Rituxan®/MabThera®
Reporting group description:	
Patients in this group received same originator rituximab version as they had received before study participation.	

Reporting group values	GP2013	Rituxan®/MabThera®	Total
Number of subjects	53	54	107
Age categorical Units: Subjects			
18-44	6	9	15
45-64	38	30	68
65 and over	9	15	24
Age continuous Units: years			
arithmetic mean	56.8	57.1	
standard deviation	± 9.91	± 12.14	-
Gender categorical Units: Subjects			
Female	46	39	85
Male	7	15	22
Race Units: Subjects			
White	51	52	103
Black	0	2	2
Asian	1	0	1
American Native or Alaska Native	1	0	1
Experienced infusion-related reactions during rituximab treatments prior to randomization Units: Subjects			
No	51	51	102
Yes	2	3	5
Weight Units: kg			
arithmetic mean	80.12	81.62	
standard deviation	± 20.22	± 20.46	-
Number of previous treatment courses with rituximab Units: treatment courses			
arithmetic mean	4.1	5	
standard deviation	± 3.32	± 3.75	-
Duration since initial diagnosis of rheumatoid arthritis			

Units: years			
arithmetic mean	13.46	14.01	
standard deviation	± 9.39	± 8.51	-
Dose of MTX at baseline			
Units: mg/week			
arithmetic mean	14.53	15.46	
standard deviation	± 6.20	± 5.14	-
C-reactive protein (CRP) at baseline			
Units: mg/L			
arithmetic mean	9.67	11.64	
standard deviation	± 24.25	± 23.63	-

End points

End points reporting groups	
Reporting group title	GP2013
Reporting group description:	
Patients in this group were switched from originator rituximab (which they received before study participation) to GP2013 - biosimilar rituximab	
Reporting group title	Rituxan®/MabThera®
Reporting group description:	
Patients in this group received same originator rituximab version as they had received before study participation.	

Primary: Hypersensitivity reactions	
End point title	Hypersensitivity reactions
End point description:	
The standardized MedDRA query (SMQ) - Hypersensitivity reactions (SMQ 20000214) was used for the identification of hypersensitivity reactions in the adverse event database.	
End point type	Primary
End point timeframe:	
24 weeks study duration	

End point values	GP2013	Rituxan®/MabThera®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: Patients				
After first infusion	3	4		
After second infusion	2	3		
Overall from first infusion	5	6		

Statistical analyses

Statistical analysis title	Analysis of hypersensitivity reactions
Comparison groups	Rituxan®/MabThera® v GP2013
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	16.9

Primary: Incidence of anaphylactic reactions

End point title	Incidence of anaphylactic reactions
End point description:	
2006 NIAID/FAAN criteria were used for identification of anaphylactic reactions	
End point type	Primary
End point timeframe:	
Within 24 hours of each study drug infusion	

End point values	GP2013	Rituxan®/Mab Thera®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: Patients				
Within 24 hours of first infusion	0	1		
Within 24 hours of second infusion	0	0		
Within 24 hours of either infusion	0	1		

Statistical analyses

Statistical analysis title	Analysis of anaphylactic reactions
Comparison groups	Rituxan®/MabThera® v GP2013
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	16.9

Primary: Incidence of potential infusion-related reactions

End point title	Incidence of potential infusion-related reactions
End point description:	
End point type	Primary
End point timeframe:	
On days of and on days after study drug infusions	

End point values	GP2013	Rituxan®/MabThera®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: Patients				
On day of or on day after first infusion	4	7		
On day of or on day after second infusion	2	5		
Overall on day(s) of or after either infusion	6	10		

Statistical analyses

Statistical analysis title	Analysis of potential infusion-related reactions
Comparison groups	GP2013 v Rituxan®/MabThera®
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	11.4

Primary: Immunogenicity

End point title	Immunogenicity

End point description:

Incidence of anti-drug-antibodies (ADA). Patients with negative ADA results at screening and at least one evaluable post-randomization ADA assessment are included in the analysis

End point type	Primary

End point timeframe:

24 weeks study duration

End point values	GP2013	Rituxan®/MabThera®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[1]	53[2]		
Units: Patients with ADA post treatment	0	1		

Notes:

[1] - Patients with a negative ADA result at screening and an evaluable post-randomization ADA assessment
[2] - Patients with a negative ADA result at screening and an evaluable post-randomization ADA assessment

Statistical analyses

Statistical analysis title	Analysis of anti-drug antibodies
Comparison groups	GP2013 v Rituxan®/MabThera®
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.2
upper limit	17.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are reported from date patient has provided informed consent and until 30 days after the patient has stopped study participation. AEs are analyzed from start date of study treatment to date of study completion/early discontinuation.

Adverse event reporting additional description:

The investigator was additionally requested to consult with the patient via phone on the next day after the infusion to document AEs, occurred within 24h of the infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	GP2013

Reporting group description:

Patients in this group were switched from originator rituximab (which they received before study participation) to GP2013 - biosimilar rituximab

Reporting group title	Rituxan®/MabThera®

Reporting group description:

Patients in this group received same originator rituximab version as they had received before study participation.

Serious adverse events	GP2013	Rituxan®/MabThera®	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	GP2013	Rituxan®/MabThera®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 53 (69.81%)	28 / 54 (51.85%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 53 (5.66%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 53 (3.77%)	2 / 54 (3.70%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 53 (1.89%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 53 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	2 / 53 (3.77%)	2 / 54 (3.70%)	
occurrences (all)	2	2	
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Osteoarthritis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	1 / 53 (1.89%)	3 / 54 (5.56%)	
occurrences (all)	1	4	
Nasopharyngitis			

subjects affected / exposed	2 / 53 (3.77%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Sinusitis			
subjects affected / exposed	2 / 53 (3.77%)	1 / 54 (1.85%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2015	After finalization of the study protocol FDA recommended to include unscheduled Anti-Drug-Antibody (ADA) blood sampling triggered by suspected immunologically related adverse events, to assess the clinical relevance of ADAs. In order to fulfill the recommendation of the methotrexate label for males on methotrexate to prevent fathering a child, respective recommendations were included in the protocol and ICF. Additionally, the informed consent procedure for following up of partner pregnancies of male study participants was introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported