CONCISE REPORT

A randomised, double-blind trial to demonstrate bioequivalence of GP2013 and reference rituximab combined with methotrexate in patients with active rheumatoid arthritis

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ABSTRACT

Objectives The aim of this report is to demonstrate pharmacokinetic (PK) and pharmacodynamic (PD) equivalence as well as similar efficacy, safety and immunogenicity between GP2013, a biosimilar rituximab, and innovator rituximab (RTX) in patients with rheumatoid arthritis (RA) with inadequate response or intolerance to tumour necrosis factor inhibitor (TNFi) treatment.

Methods In this multinational, randomised, double-blind, parallel-group study, 312 patients with active disease despite prior TNFi therapy were randomised to receive GP2013 or either the EU (RTX-EU) or the US (RTX-US) reference product, along with methotrexate (MTX) and folic acid. The primary endpoint was the area under the serum concentration–time curve from study drug infusion to infinity (AUC_{0-inf}). Additional PK and PD parameters, along with efficacy, immunogenicity and safety outcomes were also assessed up to week 24.

Results The 90% CI of the geometric mean ratio of the AUCs were within the bioequivalence limits of 80% to 125% for all three comparisons; GP2013 versus RTX-EU: 1.106 (90% CI 1.010 to 1.210); GP2013 versus RTX-US: 1.012 (90% CI 0.925 to 1.108); and RTX-EU versus RTX-US: 1.093 (90% CI 0.989 to 1.208). Three-way PD equivalence of B cell depletion was also demonstrated. Efficacy, safety and immunogenicity profiles were similar between GP2013 and RTX.

Conclusions Three-way PK/PD equivalence of GP2013, RTX-EU and RTX-US was demonstrated. Efficacy, safety and immunogenicity profiles were similar between GP2013 and RTX.

Trial registration number NCT01274182; Results.

INTRODUCTION

Rituximab (RTX) is a chimeric monoclonal IgG-1 antibody against the CD20 antigen expressed by B cells. RTX is indicated for the treatment of rheumatoid arthritis (RA) in combination with methotrexate (MTX) in patients with inadequate response to tumour necrosis factor alpha inhibitor (TNFi) therapy.[1 2] The current study compares the biosimilar GP2013 (Rixathon, Sandoz, Holzkirchen, Germany) with the reference product approved in Europe (RTX-EU; MabThera; Hoffmann-La Roche, Basel, Switzerland) and the reference product approved in the US (RTX-US; Rituxan; Genentech, San Francisco, California, USA). Comparability of GP2013 and RTX was established by extensive physicochemical and functional characterisation,[3–5] by in vitro assays as well as in vivo non-clinical studies.[6] The current study demonstrates pharmacokinetic (PK) and pharmacodynamic (PD) equivalence between GP2013, RTX-EU and RTX-US, as well as similar efficacy, safety and immunogenicity between the biosimilar and the reference product in patients with active RA.

METHODS

The study was approved by Competent Authorities and Ethics Committees. Written informed consent was obtained from all patients.

Patients

The study population consisted of adult patients with active RA refractory or intolerant to conventional synthetic disease modifying antirheumatic drugs and at least one TNFi. Main inclusion and exclusion criteria are detailed in the online supplementary table S1.

Study design and treatment

This international, randomised, double-blind study was sponsored by Sandoz, a division of Novartis. The study was conducted in 16 countries and 87 centres in Europe, USA, South-America and Asia. Eligible patients were randomised to receive a 1000 mg intravenous infusion of GP2013, RTX-EU or RTX-US on day 1 and day 15. In study part 1, patients were randomised (ratio 1:1) to receive GP2013 or RTX-EU, and in part 2 to receive GP2013 or RTX-US (ratio 1:2). Intravenous methylprednisolone 100 mg or equivalent was administered 30 min prior to each infusion. Patients also received antipyretic and antihistaminic premedication before each infusion. All patients received a stable dose of MTX (7.5 to 25 mg/week) and folic acid during the study.

Statistical analyses

The primary PK variable was area under the curve of the serum drug concentration time profiles from study drug infusion to infinity (AUC_{0-inf}). To claim

bioequivalence, the 90% CI of the ratio of the geometric mean AUCs had to be within the predefined range of 80%–125%.[7]

The main efficacy objective was to show non-inferiority of GP2013 versus RTX in terms of change from baseline in disease activity score DAS28(C reactive protein (CRP)) at week 24. Other secondary efficacy objectives included American College of Rheumatology (ACR) response rates, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Health Assessment Questionnaire Disability Index (HAQ-DI).[8–11] The main PD parameter was peripheral CD19 positive B-cell count relative to baseline, up to the second infusion (AUEC$_{0-14d}$). CD19-positive cells were used to identify CD20-positive cells as CD20 epitopes are covered by rituximab after study drug administration. Further details of statistical methodology can be found in the online supplementary text S1.

Immunogenicity assessment

A validated affinity capture elution ELISA was used for the determination of antidrug antibodies (ADAs).

Further details regarding the methods are provided in the online supplementary text S1.

RESULTS

Patient disposition and baseline characteristics

A total of 312 patients (262 female and 50 male) were randomised. Demographics and baseline clinical characteristics were comparable between the treatment arms (table 1). Patient disposition and recruitment by region are displayed in the online supplementary figure S1 and table S2.

Pharmacokinetics/pharmacodynamics

Three-way bioequivalence of GP2013, RTX-EU and RTX-US was demonstrated. The 90% CI of the ratio of the geometric mean AUCs were maintained within the predefined range of 80% to 125% for all three comparisons (table 2). Secondary PK parameters were also similar between the treatment arms. Mean AUCs were lower in all three treatment arms in ADA-positive patients (see online supplementary figure S2 and table S3).

Table 1 Demographics and baseline disease characteristics (full analysis set)

	GP2013	RTX-EU	RTX-US
	n=133	n=87	n=92
Age (years)	54.4±11.8	52.7±12.5	55.0±10.8
Age groups			
18–44 (%)	25 (18.8)	21 (24.1)	17 (18.5)
45–64 (%)	80 (60.2)	50 (57.5)	53 (57.6)
65 or more (%)	28 (21.1)	16 (18.4)	22 (23.9)
Sex, no (%) of patients			
Female (%)	111 (83.5)	73 (83.9)	78 (84.8)
Male (%)	22 (16.5)	14 (16.1)	14 (15.2)
Weight (kg)	73.2±17.0	72.5±17.2	79.5±16.5
BMI (kg/m^2)	27.4±6.2	27.3±6.0	29.7±6.6
Duration of RA (years)	10.5±8.1	10.8±7.1	11.0±8.3
Prior csDMARDs	2.3±1.7	2.1±1.1	1.9±1.2
Number of prior TNFi therapies (%)			
1 (%)	109 (82.0)	70 (80.5)	73 (79.3)
2 (%)	18 (13.5)	16 (18.4)	13 (14.1)
>2 (%)	6 (4.5)	1 (1.1)	6 (6.5)
Dose of MTX (mg/week)	15.1±4.9	14.7±5.2	15.2±5.0
Prednisolone (mg/day)	6.5±2.7	6.7±2.6	6.5±3.1
CRP (mg/L)	17.9±19.9	19.5±20.9	22.3±29.5
Erythrocyte sedimentation rate (mm/hour)	48.3±19.1	46.4±18.4	50.0±22.2
B cell count (CD19+ cells/µL)*	243±148	275±148	224±126
Serum IgG (g/L)	12.4±2.9	12.7±3.0	11.6±3.3
Serum IgM (g/L)	1.6±0.9	1.6±0.9	1.5±0.9
Serum IgA (g/L)	3.2±2.0	3.6±1.5	3.0±1.3
DAS28 (CRP)	5.8±0.9	5.9±0.9	5.9±1.0
DAS28 (ESR)	6.7±0.9	6.6±0.9	6.7±0.9
Anti-CCP antibodies (ACPA) positive (%)	120 (90.2)	75 (86.2)	86 (93.5)
RF positive (%)	126 (94.7)	81 (93.1)	86 (93.5)
Positive RF and/or anti-CCP (%)	131 (98.5)	85 (97.7)	90 (97.8)
Swollen joint count (SD)	16.0±9.1	14.8±9.2	15.0±8.1
Tender joint count (SD)	23.9±13.3	22.1±12.5	23.5±14.3
HAQ Disability Index	1.9±0.5	1.8±0.6	1.9±0.6

*In the PK set. Except where indicated otherwise, values in the table represent the mean±SD.
BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C reactive protein; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; RTX, rituximab; TNFi, tumour necrosis factor inhibitor.

Table 2 Summary of primary and key secondary PK/PD results (PK analysis set)

PK parameter (unit)	Treatment	n	Adjusted geometric mean	Comparison	Treatment comparison	
					Geometric mean ratio	90% CI of mean ratio*
Primary PK endpoints						
AUC_{0-inf} (day*µg/mL)	GP2013	124	7627.44	RTX-US vs RTX-EU	1.093	(0.989 to 1.208)
	RTX-US	80	7536.89	GP2013 vs RTX-US	1.012	(0.925 to 1.108)
	RTX-EU	79	6896.97	GP2013 vs RTX-EU	1.106	(1.010 to 1.210)
Key secondary PK endpoints						
C_{max} first inf. (µg/mL)	GP2013	120	361.53	RTX-US vs RTX-EU	1.050	(0.946 to 1.167)
	RTX-US	82	335.88	GP2013 vs RTX-US	1.076	(0.979 to 1.184)
	RTX-EU	78	319.80	GP2013 vs RTX-EU	1.131	(1.027 to 1.244)
Main PD endpoint (B cell depletion)						
$AUEC_{0-14d}$ (%*day)	GP2013	110	1226.53	RTX-US vs RTX-EU	1.033	(1.016 to 1.050)
	RTX-US	80	1240.57	GP2013 vs RTX-US	0.989	(0.974 to 1.004)
	RTX-EU	76	1201.15	GP2013 vs RTX-EU	1.021	(1.003 to 1.040)

AUC_{0-inf}, area under the serum concentration–time curve from study drug infusion to infinity; AUEC, area under the effect curve; PD, pharmacodynamic; PK, pharmacokinetic; RTX, rituximab.

A similar, rapid depletion of CD19+ peripheral B-cells was observed in all three treatment arms (figure 1). The main PD objective, demonstration of three-way equivalence of GP2013, RTX-EU and RTX-US was met, as the 90% CI of the geometric mean ratios were maintained within the standard range of 80% to 125% (table 2). Further PD data are provided in the online supplementary tables S4 and S5. Reasons of exclusion from the PK set are displayed in the online supplementary table S6. All PK/PD results are provided in the online supplementary table S7.

Efficacy
Change from baseline in DAS28(CRP) at week 24 was −2.07 (SE=0.108) and −2.11 (SE=0.095) in the GP2013 and the RTX treatment arms, respectively. The difference of 0.04 (95% CI −0.241 to 0.323) was below the predefined non-inferiority margin of 0.6. ACR20 response rate was 72.3% (95% CI 64.2% to 80.3%) and 67.3% (95% CI 59.9% to 74.7%), ACR50 response rate was 34.5% (95% CI 25.9% to 43.0%) and 40.4% (95%CI 32.7% to 48.1%), ACR70 response rate was 15.1% (95% CI 8.7% to 21.6%) and 17.3%

(95% CI 11.4% to 23.2%) in the GP2013 and RTX treatment arms at week 24, respectively. Absolute improvements in the HAQ Disability Index were −0.48 and −0.45 in the GP2013 and the RTX treatment arms at week 24. Main efficacy outcomes are shown in figure 2. Outcomes are shown separately for RTX-EU and RTX-US in the online supplementary figure S3. Low disease activity (including remission) was achieved by 40.4% and 41.8% of patients in the GP2013 arm according to CDAI and SDAI, respectively, versus 38.1% and 38.4% of patients in the RTX arm. Rheumatoid factor profiles are displayed in the online supplementary figure S4.

Safety
Three patients died during the study. One patient died of breast cancer during the screening period and was not included in the safety analysis set. One patient in the GP2013 arm died of multiorgan failure, suspected by the investigator to be related to an accidental MTX overdose by the patient (daily intake instead of weekly). A 34-year-old female patient in the RTX-US arm
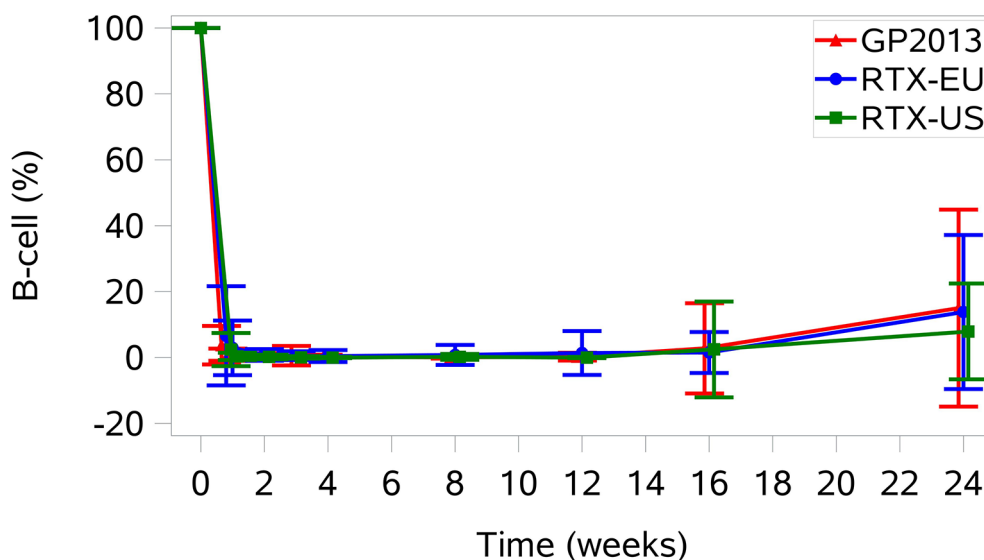
Figure 1 Arithmetic mean of B cell count relative to baseline up to week 24 (pharmacokinetic set).
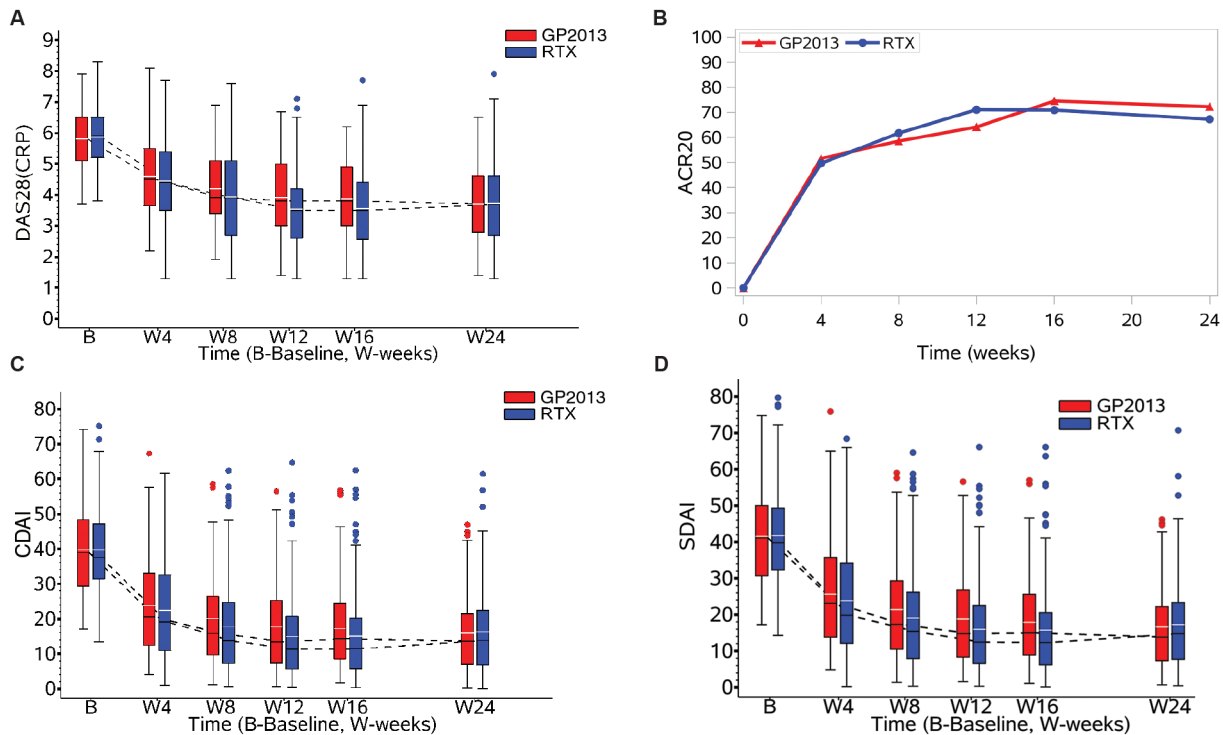
Figure 2 (A) Box whiskers plot of DAS28(CRP) up to week 24 (per protocol set). (B) ACR20 response rate up to week 24 (per protocol set). (C) Box whiskers plot of CDAI up to week 24 (per protocol set). (D) Box whiskers plot of SDAI up to week 24 (per protocol set). ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS, Disease Activity Score in 28; RTX, rituximab; SDAI, Simplified Disease Activity Index.

died of purulent pericarditis on day 20. IgG level was 11.7 g/L (normal range: 7 to 16 g/L) on day 18.

The rate of all adverse events (AEs), AEs related to the study medication, AEs leading to study drug discontinuation, serious adverse events and infusion-related reactions were similar between the treatment arms and are displayed in the online supplementary table S8. The rate of binding ADAs was 16.5% in the GP2013 versus 15.1% in the RTX group up to last patient last visit in the study. The majority of ADAs (7.1% and 9.6%, respectively) were transient, meaning that the patient had an ADA-negative sample after having ADA-positive sample(s). Five patients in the GP2013 arm, one patient in the RTX arm had neutralising ADAs. Further details regarding immunogenicity are shown in the online supplementary table S9. Changes in immunoglobulin levels were small and similar between the treatment arms (see online supplementary figure S5).

DISCUSSION

The current study is part of the stepwise demonstration of similarity of the proposed biosimilar, GP2013 and RTX. The primary objective of the study was met by demonstrating three-way PK bioequivalence of GP2013, RTX-EU and RTX-US. The data are in line with previously published RTX data.[12–20]

The study met its main efficacy objective by demonstrating non-inferiority of GP2013 versus RTX, in terms of DAS28(CRP) change from baseline at week 24. In the historic Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial, DAS28 change from baseline at week 24 was −0.34 in the placebo versus −1.83 in the RTX arm,[14] whereas in the current study improvement was −2.07 in the GP2013 and −2.11 in the RTX arm. In a recently published trial comparing the biosimilar CT-P10 and RTX, DAS28(CRP) changes were −1.95 in the CT-P10 and −2.05 in the RTX arm.[15] ACR20 response rates in the historic (REFLEX) trial, were 18% in the placebo versus 51% in the RTX

arm at 24 weeks,[14] whereas in the current study, ACR20 response rate was 72.3% in the GP2013 and 67.3% in the RTX arm. In the trial with CT-P10, ACR20 response rates were 63% in the CT-P10 and 66.7% in the RTX arm.[15]

Overall, treatment effect was numerically greater in the current study as compared with the historic data, while efficacy was similar among the treatment arms in the current study. The difference observed between trials may be attributed to differences among patient populations (e.g. in disease activity, RF positivity, number of prior TNFi). Further, in studies with active comparator, patients and investigators are aware that participants would all receive active medication.[14–16]

There were no relevant differences observed between the treatment arms in the rate or severity of adverse events. The comparison of the rate of ADAs between studies is challenging due to the differences of assay methodology but data observed was generally consistent with literature data,[14 15 20] and the rate of ADAs in the current study was shown to be similar between the GP2013 and RTX.

In summary, GP2013, a proposed rituximab biosimilar, was compared with the originator RTX. The study met its primary objective by demonstrating three-way bioequivalence of GP2013, RTX-EU and RTX-US. The study also demonstrated three-way PD equivalence, as measured by the depletion of peripheral B cells. GP2013 and RTX were shown to be similar in terms of efficacy, safety and immunogenicity.'

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Competing interests PZ, LC and TS are employees of Sandoz/Hexal. JSS, HPT, AK, AB, JG-R and MS received investigator fees from Sandoz, a Novartis Division.

Patient consent Obtained.

Ethics approval The study involved human subjects. Ethics Committee/Institutional Review Board approval was obtained. The following bodies approved the study: National Ethics Committees/Institutional Review Boards.

Provenance and peer review Not commissioned; externally peer reviewed.

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