

BRIEF REPORT

Safety and Immunogenicity of Rituximab Biosimilar GP2013 After Switch From Reference Rituximab in Patients With Active Rheumatoid Arthritis

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Objective. Comparable clinical efficacy of the rituximab (RTX) biosimilar GP2013 and reference RTX has been established in blinded randomized trials. However, when switching from a reference biologic to a biosimilar, potential safety implications are often an important consideration. Therefore, the aim of this study was to evaluate the safety of switching from reference RTX to RTX biosimilar GP2013 compared with treatment continuation with reference RTX in patients with rheumatoid arthritis (RA).

Methods. In this multinational, randomized, double-blind, parallel-group safety study, 107 patients with RA who had previously received treatment (of any duration) with reference RTX as part of routine practice and who required continuation of treatment were randomized to receive either GP2013 or to continue treatment with reference RTX. All patients received a stable dosage of methotrexate and folic acid during the study. Study assessments included the incidence of hypersensitivity, infusion-related and anaphylactic reactions, immunogenicity (antidrug antibodies), and general safety.

Results. Regardless of whether patients switched to GP2013 or continued treatment with reference RTX, the incidences of hypersensitivity (9.4% and 11.1%, respectively) and infusion-related reactions (11.3% and 18.5%, respectively) were similarly low. Only 1 patient (in the reference RTX group) developed antidrug antibodies to RTX after starting study treatment. No neutralizing antidrug antibodies were observed. Antidrug antibodies were not associated with adverse events (AEs). No clinically meaningful differences in the rate of AEs were observed between treatment groups.

Conclusion. No safety risks were detected when patients switched from reference RTX to GP2013. The safety profiles of patients in both treatment groups were similar, although the study was not powered for statistical testing of equivalence in safety.

INTRODUCTION

Biosimilars are biologic agents that match reference biologics in terms of structure, efficacy, and safety and are expected to increase patient access as well as provide savings to health care systems (1). The rituximab (RTX) biosimilar GP2013 has been

developed using a stepwise approach comprising extensive physicochemical and functional characterization followed by in vitro bioassays as well as in vivo preclinical studies (2). Equivalence of pharmacokinetics and pharmacodynamics as well as similar efficacy, safety, and immunogenicity between GP2013

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SIGNIFICANCE & INNOVATIONS

- Comparable clinical efficacy of the rituximab (RTX) biosimilar GP2013 and reference RTX has previously been demonstrated in randomized, controlled, double-blind studies. However, clinicians may be uncertain about switching from a reference biologic to an approved biosimilar, predominantly related to safety and immunogenicity.
- In this international, multicenter, randomized, controlled study in patients with rheumatoid arthritis, the safety and immunogenicity of switching from RTX to the rituximab biosimilar GP2013 was comparable with continuation of reference RTX.
- Using 3 separate instruments, a comparable incidence of specific adverse events, which could be associated with a potential immunologic response, was observed following the switch from reference RTX to the biosimilar.
- Immunogenicity of the switch was thoroughly monitored using a multi-tiered approach comprising a 3-step analysis of binding anti-RTX antibodies followed by a cell-based assay of the neutralizing capacity of anti-RTX antibodies.

and reference RTX have been demonstrated in 2 randomized, double-blind, controlled trials in patients with rheumatoid arthritis (RA) (3) and non-Hodgkin's lymphoma (follicular lymphoma) (4).

When considering a treatment switch from a reference biologic to a biosimilar, the safety profile in terms of the type, frequency, and severity of adverse events (AEs), as well as immunogenicity, are of particular interest for prescribing physicians. The potential safety implications of such a switch are currently under debate, with some regional differences in perceptions (5,6). Existing data on switching for selected biosimilar molecules have been generated from observations in open-label studies (7), extensions of approval studies (8), and from national studies performed after switches to biosimilars were mandated by decisions of local health care authorities (9,10). To date, none of the data for switching for approved biosimilars have indicated any significant concerns with respect to efficacy or safety.

The current study presents an additional step of biosimilarity assessment, providing a comparison with regard to safety and immunogenicity between either continuation of reference RTX or a switch from reference RTX to GP2013 in patients with RA.

PATIENTS AND METHODS

Patients. The study population consisted of adult patients with RA who had previously received RTX as part of routine practice and who required continuation of RTX treatment according to

the judgment of the consulting rheumatologist. There was no limitation regarding the duration of previous RTX treatment. The key inclusion and exclusion criteria are shown in Supplementary Section 1 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr23771/abstract>). The study was approved by competent authorities and ethics committees at each center. All participants provided written informed consent.

Study design and treatment. This randomized, double-blind, controlled study was conducted at 54 centers across 4 countries (US, Germany, Poland, and Hungary). After a screening period of 4–6 weeks and an evaluation of RTX antidrug antibody status at screening, eligible patients were randomized 1:1 via a central Interactive Response Technology system to receive two 1,000-mg intravenous infusions of either GP2013 or reference RTX (sourced from either the European Union or the US; as received prior to study enrollment). Randomization was stratified by region (US, European Union), antidrug antibody status at screening, and number of previous RTX treatment courses. Patients, study investigators, and other study personnel assessing outcomes and analyzing data were blinded to treatment allocation. Two intravenous infusions of study medication were administered at investigational sites on 2 consecutive visits 2 weeks apart, with intravenous methylprednisolone, antipyretic, and antihistamine premedication given prior to each infusion. All patients received a stable dosage of methotrexate (7.5–25 mg/week) and folic acid during the study.

Outcomes and data collection. Key safety end points were incidences of infusion-related reactions, anaphylactic reactions, and hypersensitivity, as well as the incidence of antidrug antibodies. Safety follow-up took place at study visits at week 2 (second infusion visit), week 12, and week 24 (end of study visits). In addition, patients were contacted remotely within the 24-hour period after each infusion to assess potential reactions to the study drug. AEs were assessed by non-directive questioning of the patient during each contact. RA disease activity was assessed according to the local routine, but data were not collected for study evaluation. However, investigators were instructed to report any lack of efficacy as an AE.

Hypersensitivity reactions were identified from the study AEs database by a Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) (11). Infusion-related reactions were identified by an SMQ of AEs occurring either on the day of or the day after GP2013/RTX infusions. Anaphylactic reactions were defined according to National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria (12), requiring the occurrence of any 2 of the following symptoms within 24 hours of the start of infusion: respiratory symptoms (e.g., dyspnea, wheeze–bronchospasm, stridor); skin/mucosal symptoms (e.g., generalized hives, itch–flush, swollen lips–tongue–uvula, throat irritation); systolic blood pressure <90 mm Hg or a decrease of >30%, or associated symptoms of reduced blood pressure; and; gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

If a patient had previously experienced an infusion-related reaction, systolic blood pressure <90 mm Hg or a decrease of >30%, or associated symptoms, would be sufficient to define an anaphylactic reaction.

Immunogenicity assessment. Blood sampling for assessing routine safety parameters and determining the presence of antidrug antibodies was performed at each study visit. Antidrug antibody sampling was also performed when any AE was considered by the investigator to be immune-related. A validated affinity capture elution enzyme-linked immunosorbent assay (ELISA) was used for the determination of antidrug antibodies, using a multi-tiered approach comprising screening, confirmation, and titration of binding RTX antidrug antibodies. Antidrug antibody-positive samples were further analyzed in a cell-based assay to assess the neutralizing capacity of the antidrug antibodies. Further methodology details are shown in Supplementary Section 2 (available

on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract>).

Statistical analysis. Due to the known low incidence of investigated key safety end points after RTX treatment in patients with RA, a prohibitively large sample size would be required to perform fully powered hypothesis testing for equivalence. Therefore, the sample size in this study was not based on statistical considerations. Descriptive statistics were used for all safety end points; point estimates and 95% confidence intervals (95% CIs) were calculated for differences in the incidence rates of key safety end points between treatment arms. Given the small sample size and low event rate observed in this study, the 95% CIs were estimated using the most conservative approach, based on the exact unconditional method (for details, see Supplementary Section 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract>). With a

Table 1. Demographics and baseline disease characteristics (safety analysis set)*

Characteristic	GP2013 (switch) (n = 53)	Reference RTX (n = 54)	Total (n = 107)
Age at screening, years	56.8 ± 9.9	57.1 ± 12.1	57.0 ± 11.0
Age group, no. (%)			
18 to <45 years	6 (11.3)	9 (16.7)	15 (14.0)
45 to <65 years	38 (71.7)	30 (55.6)	68 (63.6)
≥65 years	9 (17.0)	15 (27.8)	24 (22.4)
Female sex, no. (%)	46 (86.8)	39 (72.2)	85 (79.4)
Male sex, no. (%)	7 (13.2)	15 (27.8)	22 (20.6)
Weight, kg	80.12 ± 20.2	81.62 ± 20.5	80.88 ± 20.3
BMI, kg/m ²	29.58 ± 7.4	29.19 ± 7.6	29.38 ± 7.5
Region, no. (%)			
US	17 (32.1)	18 (33.3)	35 (32.7)
European Union	36 (67.9)	36 (66.7)	72 (67.3)
Duration of RA, years	13.5 ± 9.4	14.0 ± 8.5	13.7 ± 8.9
No. of prior biologics other than RTX	1.2 ± 1.0	1.4 ± 1.0	1.3 ± 1.0
No. of previous treatment courses with RTX	4.1 ± 3.3	5.0 ± 3.8	4.6 ± 3.6
Previous treatment courses with RTX, no. (%)			
1 course of treatment	13 (24.5)	13 (24.1)	26 (24.3)
>1 course of treatment	40 (75.5)	41 (75.9)	81 (75.7)
Time since last RTX treatment, weeks	35.8 ± 13.2	39.85 ± 15.0	37.9 ± 14.2
MTX dosage, mg/week	14.5 ± 6.2	15.5 ± 5.1	15.0 ± 5.7
Receiving steroids, no. (%)	23 (43.4)	26 (48.1)	49 (45.8)
Prednisone equivalent, mg/day†	5.4 ± 1.8	4.6 ± 2.4	5.0 ± 2.1
CRP, mg/liter (ref. range ≤5 mg/liter)	9.7 ± 24.2	11.6 ± 23.6	10.7 ± 23.8
Serum IgG, gm/liter (ref. range 6.9–14.0 gm/liter)	10.1 ± 2.1	10.2 ± 2.3	10.4 ± 2.2
Serum IgM, gm/liter (ref. range 0.34–2.4 gm/liter)	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.5
Serum IgA, gm/liter (ref. range 0.7–4.10 gm/liter)	2.4 ± 1.1	2.6 ± 1.5	2.5 ± 1.3
Anti-RTX antibody-positive at screening	1 (1.9)	1 (1.9)	2 (1.9)

* The safety analysis set consists of all patients who received the study drug at least once (all study patients). Except where indicated otherwise, values are the mean ± SD. RTX = rituximab; BMI = body mass index; MTX = methotrexate; CRP = C-reactive protein.

† Calculated based only on patients treated with glucocorticoids.

Table 2. Key safety assessments and immunogenicity (safety analysis set)*

	GP2013 (switch) (n = 53)	Reference rituximab (n = 54)	Difference, %	95% CI for difference
Hypersensitivity reactions†				
After first and before second infusion	3/53 (5.7)	4/54 (7.4)	-1.7	-20.6, 16.9
After second infusion up to end of study	2/51 (3.9)	3/54 (5.6)	-1.6	-20.9, 17.3
Overall from first infusion up to end of study‡	5/53 (9.4)	6/54 (11.1)	-1.7	-20.6, 16.9
Severe	1/53 (1.9)§	0		
Anaphylactic reactions¶				
Within 24 hours of either infusion	0	1/54 (1.9)	-1.9	-20.6, 16.9
Infusion-related reactions#				
First infusion	4/53 (7.5)	7/54 (13.0)	-5.4	-24.2, 13.3
Second infusion	2/51 (3.9)	5/54 (9.3)	-5.3	-24.5, 13.6
Overall‡	6/53 (11.3)	10/54 (18.5)	-7.2	-26.0, 11.4
Severe	1/53 (1.9)§	0		
Antidrug antibodies**				
Antidrug antibody positivity post-treatment	0	1/53 (1.9)	-1.9	-21.2, 17.6

* The safety analysis set consists of all patients who received the study drug at least once (all study patients). Values are the number of patients/number of patients assessed (%). 95% CI = confidence interval.

† Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query was used to identify hypersensitivity reactions in the database of adverse events.

‡ Patients with reactions after both infusions are counted only once in this category.

§ One patient with fatigue, fever, and muscle pains reported as being serum sickness was withdrawn after the first infusion. This patient is listed under both hypersensitivity and infusion-related reactions based on study methodology.

¶ 2006 National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria were used to define anaphylactic reactions within 24 hours of the start of GP2013/rituximab infusions.

MedDRA Query was used to identify infusion-related reactions in the database of adverse events occurring on the day of or day after GP2013/RTX infusions.

** Patients with negative results of antidrug antibody testing at screening and at least an evaluable post-randomization antidrug assessment were included in the analysis.

sample size of 100 patients (50 patients per treatment group), the expected upper limits of the 95% CIs for the incidence differences between treatment groups were 10.3% for hypersensitivity, 3.9% for anaphylaxis, 17.0% for infusion-related reactions, and 11.2% for the incidence of antidrug antibodies. In the safety analysis, any difference between treatment groups that exceeded the respective upper limit value would be considered a statistically significant signal of potential difference in the specific end point. Calculations were based on the assumption that no difference would be observed between treatment groups, and based on the incidences of safety end points as observed both in previous literature or in prior studies of GP2013: hypersensitivity, 7.5%; anaphylaxis, 1%; infusion-related reactions, 17.0%; and immunogenicity, 9%.

RESULTS

Patient disposition and baseline characteristics. A total of 107 patients (85 female and 22 male) were randomized to either switching to GP2013 (n = 53) or continuing reference RTX (n = 54). All randomized patients received the first infusion, but in the switch group, 2 patients withdrew before the second infusion

(1 experienced a hypersensitivity reaction, and 1 withdrew informed consent).

The demographics and baseline clinical characteristics were comparable between the treatment groups (Table 1). Patient disposition and recruitment by region are shown in Supplementary Figure 1 and Supplementary Table 1, respectively (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract>).

Key safety assessments. The incidences of 3 types of reaction were used in the study to thoroughly assess the incidence of AEs that might be associated with the switch from reference RTX to the biosimilar RTX GP2013: anaphylactic reactions at any study time point; hypersensitivity reactions at any study time point; and infusion-related reactions, occurring either on the day of or day after each infusion. A degree of redundancy was observed between these 3 safety instruments, which therefore represent a conservative approach to identify any potential safety risks.

Only 1 patient in the RTX group experienced a combination of AEs fulfilling the criteria for anaphylaxis (mild throat irritation as-

sociated with a decrease in systolic blood pressure and mild vomiting). The incidence of hypersensitivity reactions was similarly low in both treatment groups (Table 2) and was slightly lower after the second infusion. Overall, the majority of hypersensitivity events were mild. Serum sickness with symptoms of fatigue, fever, and muscle pain—the only event that defined severe hypersensitivity—occurred in 1 patient from the switch group, leading to study drug discontinuation. All hypersensitivity reactions are shown in Supplementary Table 2 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract>). The incidence of infusion-related reactions was higher in the RTX group (Table 2). The severity of most events was mild, and no cluster of particular AEs was observed. All infusion-related reactions are shown in Supplementary Table 3 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract>).

Immunogenicity. In total, antidrug antibody samples were missing for only 2 patients (at 1 visit each), meaning that 99.5% of planned antidrug antibody samples were collected and analyzed. The 2 patients who tested antidrug antibody–positive at screening (1 in each group) were antidrug antibody–negative at all post-screening visits, whereas 1 patient in the RTX group who was antidrug antibody–negative at screening was antidrug antibody–positive at all visits after the start of treatment. No AEs were reported for this patient throughout the study. All antidrug antibodies were non-neutralizing. The only patient with severe hypersensitivity (serum sickness) in the switch group was antidrug antibody–negative at all visits. The patient in the RTX group who had an anaphylactic reaction during the first infusion was antidrug antibody–positive at screening but antidrug antibody–negative at all subsequent visits.

Standard safety assessments. There was a low incidence of serious AEs (SAEs), all of which occurred only in the RTX group. One patient died in the RTX group due to cardiopulmonary failure, which was not suspected to be related to the study drug. AEs were reported in more patients in the switch group, while more patients in the RTX group experienced severe AEs. In all system organ classes with numerical imbalances in incidence between treatment groups, no cluster of specific events could be observed (Figure 1). Arthralgias, reported only in the switch group, involved large joints in 2 of 3 patients, both of whom presented with osteoarthritis at study initiation. None of the infections was reported as serious or severe, and no opportunistic infections occurred. Only 1 patient withdrew due to safety reasons (Figure 1).

DISCUSSION

In this study, we evaluated the safety of switching from reference RTX to the biosimilar RTX GP2013. To our knowledge, this is the only randomized switching study to date enrolling pa-

tients who were treated with RTX as part of routine practice or within clinical studies, without any limitation to previous treatment duration.

The key safety end points of this study (anaphylaxis, hypersensitivity, infusion-related reactions, and immunogenicity) were chosen to assess a potential immunologic response following a switch from reference RTX to the biosimilar. The end points selected assessed this potential response from different perspectives and with a certain degree of redundancy. The results for the key safety end points did not show any clinically meaningful differences between treatment groups, and the incidences were similarly low. The reason for the low incidence of infusion-related reactions in this study could be attributed to the high number of RTX treatment courses previously administered to patients. According to the literature, most serious infusion-related reactions occur during the first infusion of RTX (13). Patients in this study had, on average, 4–5 courses of RTX treatment before the start of the study. There were very few SAEs in the study, and none were observed in the switch group. The differences in the incidence of AEs in individual categories could not be attributed to a cluster of specific events, while certain imbalances were already observed among comorbidities at the time of study initiation.

Immunogenicity was rigorously monitored during the study, because an almost complete set of serum samples was obtained from all patients at all visits. Only 1 patient in the RTX group developed antidrug antibodies after the start of treatment, which is less than the known incidence of antidrug antibodies in patients receiving RTX treatment. However, the literature indicates that the occurrence of antidrug antibodies to RTX decreases with repeated treatments (14,15). In the current study, post-treatment antidrug antibodies were not linked to any AEs. In particular, patients experiencing serum sickness and anaphylaxis were antidrug antibody–negative post-treatment. Furthermore, no antidrug antibodies were detected in any patient in the switch group, suggesting that the switch from reference RTX to the biosimilar is not associated with increased immunogenicity.

It is known that results of biosimilar switching studies depend to a certain extent on the study design. Although some open-label studies have shown an increased number of withdrawals or AEs following a switch (7,10), these effects were less frequently observed in randomized studies (8,9), suggesting the potential occurrence of a “nocebo” effect resulting from negative expectations toward the biosimilar (10).

The small sample size is another known factor that potentially contributes to imbalances in the baseline characteristics of patients, which might consequently lead to imbalances in AEs related to comorbidities. However, to adequately power a comparison of safety end points that have a very low incidence (e.g., anaphylaxis $\geq 1/1,000$ to $< 1/100$) would have required enrollment of a prohibitively high number of patients. Definition of equivalence margins for major safety events is also challenging, resulting in descriptive analyses of safety end points

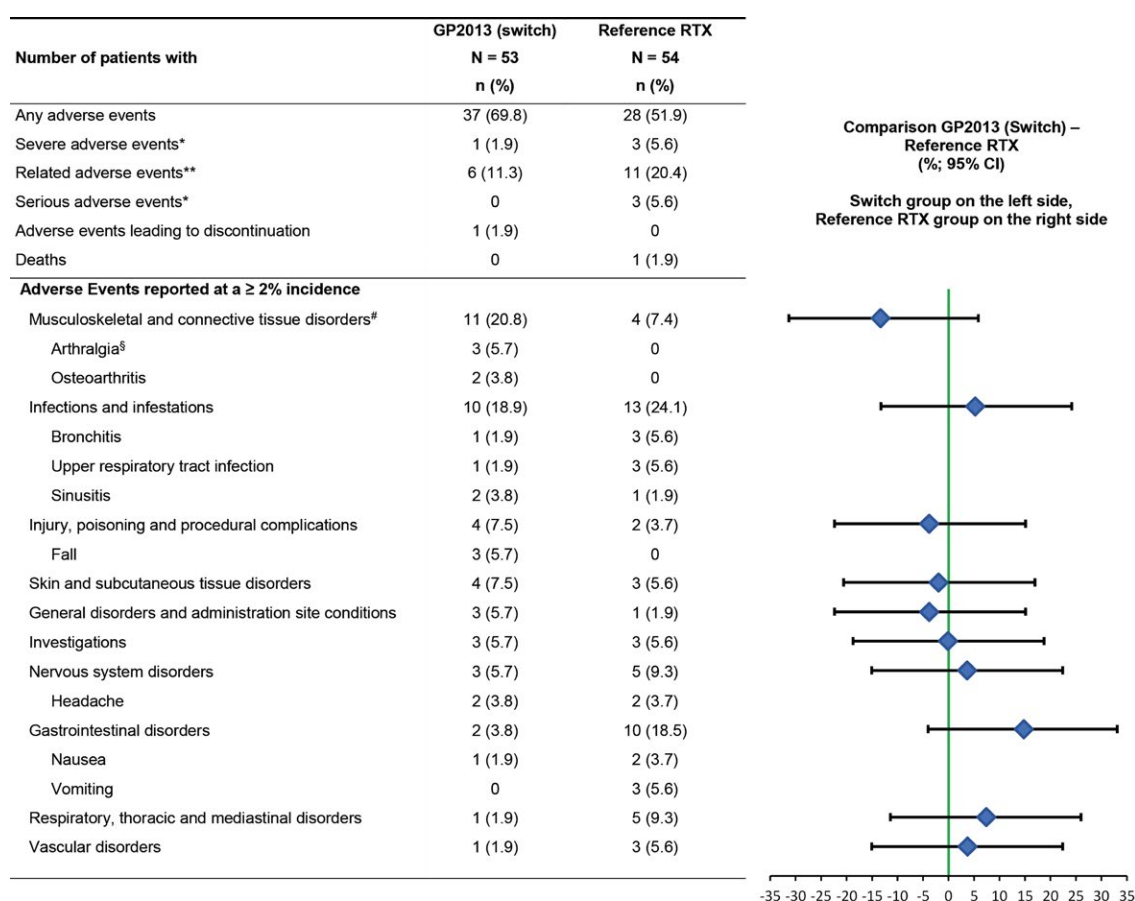


Figure 1. Summary of adverse events (safety analysis set). * The severity of adverse events was assessed by study investigators according to the study protocol. An adverse event was considered severe if it prevented the patient's normal activities. ICH GCP definition of seriousness of adverse event criteria was applicable. **As suspected by the study investigator. [#]MedDRA system organ classes (SOC). [§]MedDRA Preferred terms (PT). CI = confidence interval; GCP = Good clinical practice; ICH = International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with an adverse events after the infusion; N = total number of patients who received the respective infusion; RTX = rituximab. Safety analysis set consists of all patients who received study drug at least once (all study patients).

generally being used in biosimilar trials, including other trials investigating treatment switches from a reference biologic to a biosimilar (8–10). Introduction of a certain level of redundancy by evaluating different immunologic end points after the switch, as done in this study, increases the robustness of the safety assessment.

Stratification by region, antidrug antibody status at screening, and number of prior RTX treatment courses was used to improve balance of these important factors across treatment groups, but given the small sample size, this may have compromised balance in other factors. Furthermore, although the study was performed at multiple centers and across several countries, a low number of patients were included at each site, which might have led to selection bias. Nonetheless, the fact that the inclusion/exclusion criteria were consistent with RTX label recommendations supports the notion that this study adequately represents a real-world scenario of patients transitioning to a biosimilar, as would be performed by health care professionals.

In summary, the results of this study demonstrate that treatment switch from reference RTX to the biosimilar GP2013 in RA patients previously treated with RTX as part of routine practice has a safety profile comparable to continuation of reference RTX. No additional safety risks were detected in patients who switched from reference RTX to GP2013.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Tony had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tony, Kollins.

Acquisition of data. Krüger, Schulze-Koops, Kivitz, Jeka, Verecke.

Analysis and interpretation of data. Krüger, Cohen, Schulze-Koops, Kivitz, Jeka, Verecke, Cen, Kring, Kollins.

ROLE OF THE STUDY SPONSOR

Sandoz facilitated the study design, provided writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Editorial assistance was provided by Ben Caldwell (Spirit, Manchester, UK) and funded by Hexal AG, a Sandoz company. Publication of this article was not contingent upon approval by Sandoz.

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1 Safety and Immunogenicity of Rituximab Biosimilar GP2013 After Switch from Reference
2 Rituximab in Patients with Active Rheumatoid Arthritis

3 **Supplementary material**

5 **Supplementary section 1: Inclusion and exclusion criteria**

6 ***Main inclusion criteria***

- 7 • Male patients, or non-pregnant, non-lactating female patients, at least 18 years of
8 age at screening, who provided written informed consent before any assessment
9 was performed.
- 10 • Rheumatoid arthritis according to American College of Rheumatology [ACR] 2010
11 criteria.
- 12 • At least one full treatment course of reference rituximab for the therapy of
13 rheumatoid arthritis, 6 to 18 months prior to randomization.
- 14 • Eligible for a subsequent treatment course of rituximab according to the clinical
15 judgment of the investigator.
- 16 • Stable dose of methotrexate and folic acid for at least 4 weeks prior to
17 randomization.

18 ***Main exclusion criteria***

- 19 • RA functional status class IV (ACR 1991 revised criteria)
- 20 • Treatment with any biologics for any indication since the start of last treatment with
21 rituximab
- 22 • History of severe hypersensitivity to rituximab, which required drug discontinuation

- 1 • Previously treated with any cell depleting therapies, including investigational agents
- 2 • Known severely immunocompromised state
- 3 • Active systemic infection
- 4 • Immunoglobulins below lower limit of normal (LLN)
- 5 • Positive serology for hepatitis B or hepatitis C infection
- 6 • History of cancer

7 **Supplementary section 2: Methodology**

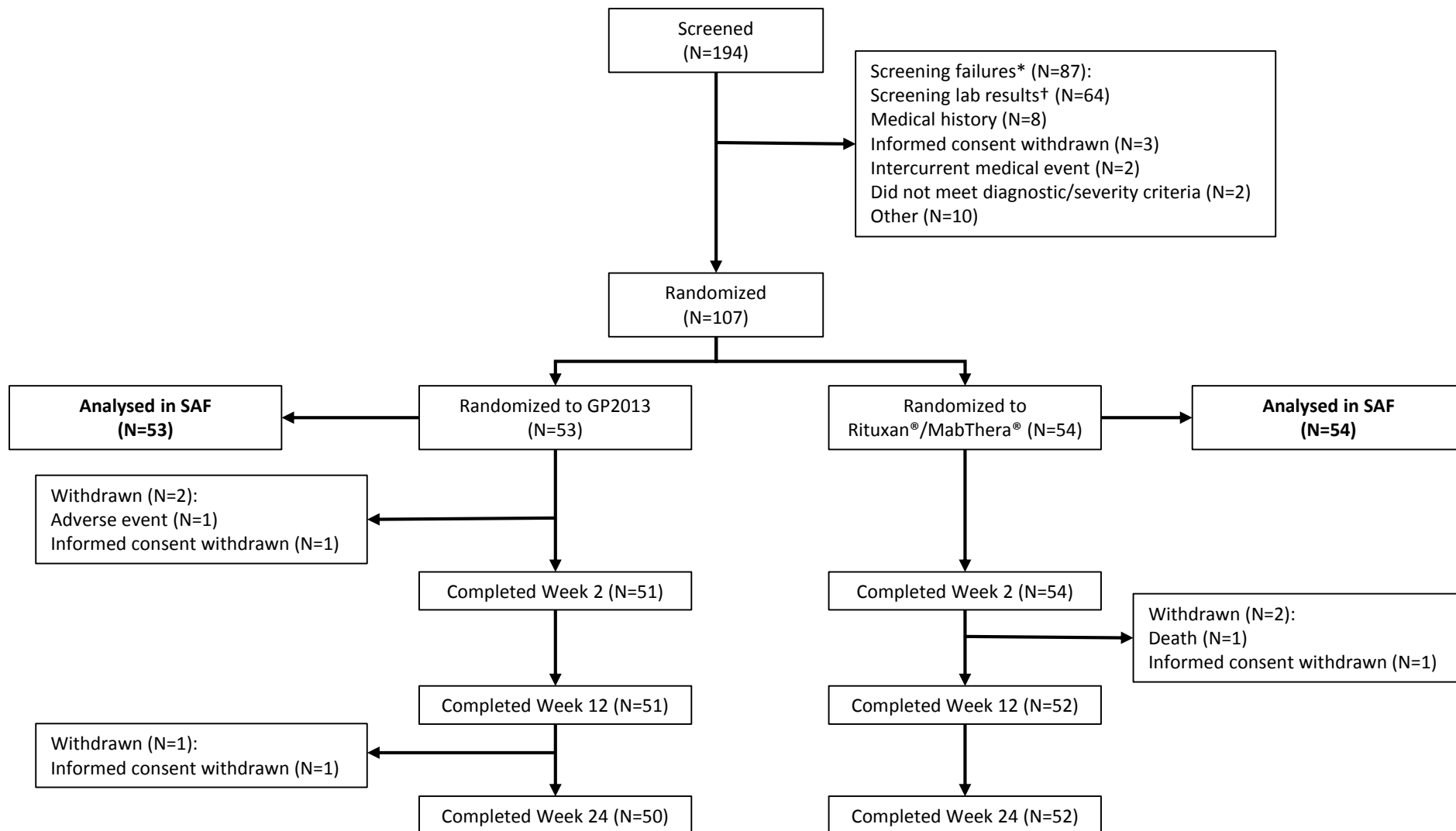
8 Hypersensitivity reactions were identified from the study adverse events (AEs) database
9 by a Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ).
10 SMQs are validated, pre-determined sets of MedDRA terms grouped together to define
11 specific medical conditions. They are developed and maintained by the Council for
12 International Organizations of Medical Sciences (CIOMS) Working Group.¹ Infusion-
13 related reactions were identified by a standardised Novartis MedDRA query among the
14 AEs that occurred on the day of or day after GP2013/RTX infusions. Novartis MedDRA
15 Queries (NMQs) are a collection of MedDRA terms, defining a specific medical concept,
16 which is not covered by an existing MedDRA SMQ. NMQs are compiled and governed
17 by a company crossfunctional MedDRA team in accordance with the established
18 process. Descriptive statistics were used for all safety endpoints; point estimates and
19 95% CI were calculated for differences in incidence rates of key safety endpoints
20 between treatment arms. Given the small sample size and low event rate observed in
21 this study, the 95% CIs were estimated using the most conservative approach based on
22 the exact unconditional method.²

Immunogenicity assessment: Detection of binding and neutralising anti-drug antibodies

The immune response after rituximab administration was evaluated by a multi-tiered approach comprising an immunogenicity assay for the screening, confirmation and titration of binding anti-rituximab antibodies (ADAs) and an assay for the assessment of the neutralising capacity of antibodies (neutralising antibody [NAb] assay). The methods were validated according to international guidelines.

In brief, in the first step, serum samples were screened for antibodies capable of binding rituximab in a screening ELISA. In the second step, to prove the specificity of the ADAs detected in the screening assay, all samples with a result equal to or above the screening cut-point were analysed in a confirmatory ELISA. Only samples above the confirmatory cut-point were reported as ADA-positive, otherwise as ADA-negative. The titer of confirmed positive samples as well as their neutralising capacity was determined subsequently. The evaluation for NAb was performed in a cell-based complement-dependent cytotoxicity (CDC) assay. The NAb assay format was based on the effector function of rituximab where the presence of NAb prevent rituximab from inducing CDC response.

Figure S1. Patient disposition



SAF, safety analysis set

*Patient can have more than one reason for screening failure

†Lab results leading to screening failure are mainly due to serum immunoglobulins below the reference range

Table S1: Number of patients randomised by region

Country	Number of patients screened N=194	Number of patients randomised N=107	Number of patients withdrawn from study after randomisation N=5
Germany	85	50	1
Hungary	17	11	1
Poland	15	11	0
US	77	35	3

Table S2: Number (%) of patients with hypersensitivity reactions after first infusion up to end of study.

MedDRA Preferred Term	GP2013 (switch) N=53 n (%)	Reference RTX N=54 n (%)
Regardless of study drug relationship		
Any hypersensitivity reaction	5 (9.4)	6 (11.1)
Asthma	1 (1.9)	1 (1.9)
Eczema	1 (1.9)	0
Pruritus allergic	1 (1.9)	0
Rash pustular	1 (1.9)	0
Serum sickness	1 (1.9)	0
Erythema	0	1 (1.9)
Flushing	0	1 (1.9)
Pruritus	0	2 (3.7)
Seasonal allergy	0	1 (1.9)
Suspected to be related to study drug		
Any hypersensitivity reaction	2 (3.8)	2 (3.7)
Pruritus allergic	1 (1.9)	0
Serum sickness	1 (1.9)	0
Pruritus	0	2 (3.7)

The standardized MedDRA query (SMQ) 'Hypersensitivity reactions' was used for the identification of hypersensitivity reactions in the adverse event (AE) database. AEs identified as hypersensitivity reactions according to the SMQ irrespective of suspected relationship to study drug as well as suspected by the investigators to be related to study drug are included in this table. Preferred terms are sorted by descending frequency, as reported in the switch group column. A patient with multiple occurrences of an AE for a preferred term under one treatment is counted only once.

Table S3: Number (%) of patients with infusion-related reactions on day of or on day after either infusion.

MedDRA Preferred Term	GP2013 (switch) N=53 n (%)	Reference RTX N=54 n (%)
Regardless of study drug relationship		
Any infusion-related reaction	6 (11.3)	10 (18.5)
Arthralgia	1 (1.9)	0
Dysgeusia	1 (1.9)	0
Malaise	1 (1.9)	0
Nausea	1 (1.9)	1 (1.9)
Pruritus allergic	1 (1.9)	0
Serum sickness	1 (1.9)	0
Diarrhoea	0	1 (1.9)
Dizziness	0	1 (1.9)
Erythema	0	1 (1.9)
Flushing	0	1 (1.9)
Headache	0	2 (3.7)
Oral pruritus	0	1 (1.9)
Pruritus	0	2 (3.7)
Pyrexia	0	1 (1.9)
Throat irritation	0	1 (1.9)
Vomiting	0	2 (3.7)
Suspected to be related to study drug		
Any infusion-related reaction	3 (5.7)	8 (14.8)
Malaise	1 (1.9)	0
Pruritus allergic	1 (1.9)	0
Serum sickness	1 (1.9)	0
Dizziness	0	1 (1.9)
Headache	0	1 (1.9)
Nausea	0	1 (1.9)
Oral pruritus	0	1 (1.9)
Pruritus	0	2 (3.7)
Pyrexia	0	1 (1.9)
Throat irritation	0	1 (1.9)
Vomiting	0	1 (1.9)

Novartis MedDRA Query (NMQ) was used to identify infusion-related reactions in the database of Adverse Events that occurred on the day of or day after GP2013/RTX infusions.

AEs identified as infusion-related reactions according to the NMQ are included in this table, regardless of study drug relationship as well as suspected by the investigators to be related to study drug.

Preferred terms are sorted by descending frequency, as reported in the switch group column.

A patient with multiple occurrences of an AE for a preferred term under one treatment is counted only once.

References for the supplementary section

1. International Council for Harmonisation of Technical Requirements for pharmaceuticals for Human Use (ICH) (formerly International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.0. 2015.
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