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Comparing immunogenicity and safety following transition from reference rituximab to biosimilar rituximab (DRL_RI) in patients with rheumatoid arthritis: a randomized, double-blind, phase 3 study

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Abstract

Objectives To assess immunogenicity and safety in patients with active rheumatoid arthritis (RA) transitioning from rituximab [US-licensed rituximab: Reference Product (RP); EU-approved rituximab: Reference Medicinal Product (RMP)] to DRL_RI (proposed rituximab biosimilar), in comparison to those continuing on RP/RMP.

Methods This double-blind, randomized, Phase 3 study included 140 RA patients having prior exposure to RP/RMP; transitioned to DRL_RI ($n=70$) or continued with RP/RMP ($n=70$) for two 1000 mg infusions on Days 1 and 15. Assessments included Time-matched Rituximab Concentration (TMRC), anti-drug antibodies (ADAs), neutralizing antibodies (NAbs) and ADA titre over 12 weeks, and safety follow-up till 26 weeks.

Results The mean age of subjects was 59.8 years (range: 24, 86) and the mean BMI was 27.76 kg/m^2 (range: 17.5, 52.0). Incidence of ADA after dosing was low in both groups: 1.4% in DRL_RI group on Day 15, Week 8, and Week 12; and 2.9% in RP/RMP group at Week 12. Only 1 patient in DRL_RI group was positive for NAbs at Week 8. ADA titre values did not significantly differ between the two groups. The time-matched rituximab concentration was comparable between groups, indicating no interference for immunogenicity assessment. Treatment-emergent adverse events (TEAEs) were reported by 34.3% and 38.6% patients, respectively, in DRL_RI and RP/RMP groups. Incidences of TEAEs that were drug-related, leading to treatment discontinuation, grade ≥ 3, or serious, were also comparable.

Conclusion Immunogenicity was low and comparable in RA patients transitioning to DRL_RI or continuing on RP/RMP. The overall safety profile in patients transitioning to DRL_RI did not appear to differ in frequency, severity, or quality from patients continuing on RP/RMP and was in line with the known safety profile of rituximab.

Trial registration ClinicalTrials.gov identifier NCT0426877 EudraCT:2019-002810-37 US IND 112766.

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Key messages

• Immunogenicity and safety in patients with active RA transitioning from reference rituximab to DRL_RI (biosimilar rituximab) were comparable to those continuing with reference rituximab.

• Incidence of ADA after dosing was low and similar between patients transitioning to DRL_RI vs. continuing with reference rituximab.

• Adverse events in patients who transitioned to DRL_RI or continuing treatment with the reference rituximab were comparable, and overall, in line with the known safety profile of rituximab.

Keywords Rituximab, Rheumatoid arthritis, Biosimilar, Transition, Immunogenicity, Safety, Switching

Introduction

Rheumatoid arthritis (RA) is an immune-mediated disease of the joints, characterized by chronic inflammation and synovial hyperplasia eventually leading to cartilage and bone destruction. At the advanced stage, RA leads to deformities and bone erosion, which are usually very painful for the patient [1, 2]. DMARD treatment should be started as soon as a diagnosis of RA has been made. However, a diagnosis of RA in its earliest stage is not always easy and a suspected diagnosis of RA may be sufficient to initiate DMARD treatment. Importantly, American College of Rheumatology (ACR) and EULAR have collaboratively developed new criteria that are pertinent for this early phase of the disease [3]. The addition of biologic disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) to conventional synthetic DMARDs (csDMARDs) has been a major advancement in the management of RA patients [4]. Rituximab is an effective therapy in patients with RA and inadequate response to one or more TNF antagonist therapies.

Rituximab [Rituxan®; US-licenced rituximab: *hereafter referred to as Reference Product (RP)*, and MabThera®; EU-approved rituximab: *hereafter referred to as Reference Medicinal Product (RMP)*], a genetically engineered chimeric murine/human monoclonal immunoglobulin G1 (IgG1) kappa antibody directed against the B- lymphocyte antigen cluster of differentiation (CD) 20, is an innovator bDMARD approved for the treatment of RA [5–7]. Dr. Reddy's Laboratories S.A. (DRL) has developed a proposed biosimilar of rituximab – DRL_RI. DRL has conducted extensive evaluation to demonstrate similarity of structural, physicochemical, analytical, and functional characteristics of DRL_RI with the reference products (*data on file*), DRL_RI has also demonstrated a three-way pharmacokinetic (PK) similarity with the originator rituximab (RP/RMP) and comparable efficacy, pharmacodynamic (PD), safety, and immunogenicity in a Phase 1/2 study in RA patients who had inadequate response to methotrexate (MTX)- based therapy and no prior biologic administration [8]. A clinical study in diffuse large B-cell lymphoma (DLBCL) patients demonstrated similar Pharmacokinetics (PK), Pharmacodynamics (PD) efficacy, safety, and immunogenicity profiles of DRL_RI and RMP [9]. In addition, a clinical study in low tumour burden follicular lymphoma (LTBFL) patients confirmed efficacy equivalence between DRL_RI and RMP. This study also demonstrated similar Pharmacokinetics (PK), Pharmacodynamics (PD), safety, and immunogenicity profiles of DRL_RI and RMP (data on file).

When a biosimilar product is commercialized, it is expected that some patients will transition from the currently marketed reference product to the biosimilar product. Hence, it is important to rule out any impact of this transition on safety and immunogenicity in patients. This is also a regulatory requirement. This Phase 3 study (RI-01-007) was conducted to assess the immunogenicity and safety of patients with active RA who were previously treated with RP/RMP but were transitioned to DRL_RI as compared with those continuing treatment with reference biologic.

Methods

Study design

This was a randomized, double-blind, parallel-group, multicentre, Phase 3 design (Fig. 1). Patients with active RA who were on treatment with RP/RMP were included across 46 centres in 7 countries (Bulgaria, Czech Republic, Germany, Hungary, Lithuania, Poland, US) between January 2020 and April 2022 (ClinicalTrials.gov identifier: NCT0426877; EudraCT: 2019-002810-37; US IND: 112766). The study was conducted in accordance with Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by the respective regulatory agencies, and ethics committees at each participating centre. All participating patients provided written informed consent.

The study period included 14 days of screening, followed by 12 weeks of double-blind period and a safety follow-up up to week 26. Patients were randomized, using block randomization and stratification by region (US/EU), in a 1:1 ratio to either transition to DRL_RI or continue treatment with RP/RMP. Study visits were scheduled at Weeks 2, 4, 8, and Week 12 (end of study), and a safety follow-up visit (with pregnancy testing only for eligible patients) at Week 26.

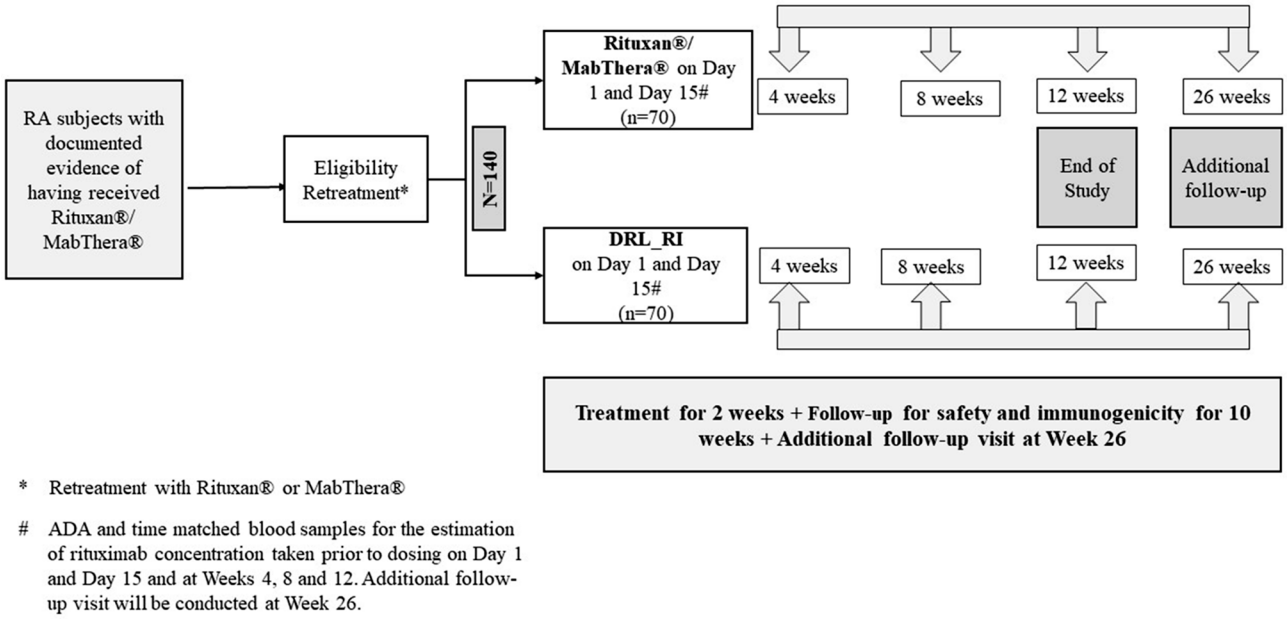

Fig. 1 Study Design. Abbreviations: ADA, anti-drug antibody; DRL_RI, biosimilar rituximab; N, total number of patients; n, number of patients in each treatment group; RA, rheumatoid arthritis

The study conduct was impacted by the COVID-19 pandemic situation since January 2020. Applicable measures against COVID-19 as recommended by US Food and Drug administration (US FDA) and European Medical Agency (EMA) were implemented at all sites. The impact of COVID-19 on the study was evaluated and reported.

Study population

Male or female patients aged > 18 years with active RA, who had received at least 1 full course comprising of two 1000 mg infusions with either RP or RMP (at least 16 weeks or 24 weeks prior to randomization, respectively, as per the respective country prescribing information], and who were taking a steady dose of weekly methotrexate (MTX) (7.5 mg to 25 mg) and folic acid (at least 5 mg per week) for at least 4 weeks before randomization, were included. Patients were excluded if they had RA functional Class IV; had received prior treatment with rituximab except RP/RMP, were on other biologic DMARDs, or janus kinase (JAK) inhibitors administered within 12 weeks before the first dose of rituximab.

Patient eligibility (inclusion and exclusion) criteria are listed in the Supplementary Data S1.

Study treatments

Patients received two 1000 mg IV infusions of either DRL_RI or RP/RMP, on Day 1 and Day 15, administered using the escalating infusion rate as per approved product labels. Approved prophylactic medications were administered, and infusion rate was well-controlled to reduce the incidence of serious infusion-related reactions (IRRs). Pre-medications included an antipyretic [paracetamol (acetaminophen)], an antihistaminic (diphenhydramine), 100 mg IV methylprednisolone or its equivalent at least 30 min prior to rituximab infusions. Patients were maintained on folic acid and a stable dose of ongoing weekly MTX. Low-dose corticosteroids (≤10 mg/day prednisone equivalent) and nonsteroidal anti-inflammatory drugs [*paracetamol (acetaminophen) was considered as an antipyretic and not nonsteroidal anti-inflammatory drug in this study*], were permitted.

Study assessments and endpoints

The immunogenicity endpoint was defined as the incidence of anti-drug antibody (ADA), ADA titre and neutralizing antibody (NAb), measured over 12 weeks. Blood samples for ADA (including NAb) were collected pre-dose (within 30 min) of study drug infusion on Days 1 and 15, and post-dosing at Weeks 4, 8, and 12. Blood sampling for the time-matched rituximab concentration (TMRC) analysis was also done.

ADA, NAb testing and titre determination

Only patients who were ADA positive at both, the screening assay and confirmatory test during the study, were analysed for presence of NAb. The ADA methodology was based on the principle of capture of the ADA by the drug and detection by biotin-labelled drug, using enzyme-linked immunosorbent assay (ELISA). Confirmatory test involved inhibition of the response seen in screening assay with high drug concentration. The assay

format was an adaptation of screening assay. Samples that showed a response ≥ the pre-determined screening cut point were called "screening positive". Titres were determined by a semi-quantitative assay. Serial 2-fold dilutions of confirmed positive samples were performed and the reciprocal of the dilution that yielded a response at or above the titration cut point was reported as the ADA titre. NAb assay considered that sample containing NAbs would reduce or abolish the biological activity associated with a known concentration of drug product used in a cell-based NAb assay.

Safety endpoints

Primary safety endpoints included incidences of TEAEs, serious adverse events (SAEs), anaphylactic reactions, hypersensitivity reactions, and IRRs, assessed till Week 26. Any adverse event (AE) related to confirmed COVID-19 was considered an event of special interest (EOSI). All AEs were classified by the Medical Dictionary for Regulatory Activities (MedDRA) (Version 25.0) system organ class and preferred term.

Statistical analysis

A total of 140 patients were randomly assigned to receive DRL_RI or RP/RMP. Statistical analyses were conducted using SAS® software (SAS Institute, Cary, NC, USA) Version 9.4. Safety population included all patients who were randomized and received at least one dose of study drug. Immunogenicity population included all participants with at least one post-dose ADA assessment result available. TMRC population included all patients who received at least one dose of the study drug and had a valid TMRC concentration available. Continuous data were described using descriptive statistics i.e., n, mean, standard deviation [SD], median, quartiles, minimum, and maximum; and categorical data using the count and percentages.

Results

Patient disposition and demographics

A total of 224 patients were screened, of which, 140 patients were randomized to receive DRL_RI ($n=70$) or RP/RMP [RP for those already on RP ($n=22$) and RMP for those already on RMP ($n=48$) before study entry]. Data for RP/RMP was pooled into one group for comparison with the DRL_RI group. Of the enrolled 140 patients, 138 (98.6%) patients completed study treatment; 2 (2.9%) patients were discontinued from DRL_RI group– one due to an AE, and one due to consent withdrawal. In all, 134 (95.7%) patients completed the study till Week 12, and 118 patients re-consented for Week 26 follow-up visit. Of these, 116 (98.3%) patients completed Week 26 follow-up: 57 [96.6%] patients from DRL_RI group and 59 [100%] patients from RP/RMP group. Treatment compliance and trial discontinuation between groups were similar. All 140 enrolled patients (70 patients from each group) were included in Safety Population. Immunogenicity and TMRC populations included 137 (97.9%) patients: 69 [98.6%] from DRL_RI and 68 [97.1%] from RP/RMP groups (CONSORT Flow Chart Fig. 2). COVID-19 related protocol deviations occurred in 18 (12.9%) patients; the most frequent significant deviation was missing endpoint assessments in 4 (5.7%) patients of DRL_RI group and 5 (7.1%) patients of RP/RMP group.

Patient demographics and baseline characteristics were comparable between groups (Table 1). The mean (SD) age of patients was 59.8 (11.7) years [range: 24, 86 years] and mean (SD) body-mass index (BMI) was 27.8 (6.2) kg/m^2. The majority of patients were female (82.1%), postmenopausal (71.1%), *White* (99.3%), and '*Not Hispanic or Latino*' (88.6%). Most patients (67.9%) were recruited from Europe. In all, 122 (87.1%) patients—63 (90.0%) patients in DRL_RI group and 59 (84.3%) patients in RP/RMP group—reported at least one medical condition/surgery at baseline; hypertension, osteoarthritis, and osteoporosis were common. The median duration of RA at randomization was 112 months, and median time from prior rituximab treatment was 6.6 months (mean: 7.6 months). Overall, 45 (32.1%) patients had prior exposure to RP and 95 (67.9%) patients to RMP. Fewer patients [(47 (33.6%)] received one prior course of rituximab and majority of patients [93 (66.4%)] received more than one prior course of rituximab.

All 140 patients received Day 1 dose, and 137 patients received Day 15 dose — 69 patients received DRL_RI, 22 patients received RP and 46 patients received RMP. Day 1 dose was interrupted in 1 patient in DRL_RI group due to IRR, and in 1 patient in RP/RMP group due to hypersensitivity. Common concomitant medications were folic acid (97.1% in both groups), MTX (100% in both groups), and cholecalciferol (34.3% in DRL_RI and 22.9% in RP/RMP group). About 41% patients in each group received systemic glucocorticoids. One patient in DRL_RI group received methylprednisolone and one patient in RP/RMP group received triamcinolone as a rescue medication. One (1.4%) patient from DRL_RI group received re-dosing of rituximab (*Truxima*®, a rituximab biosimilar) at the end of the study visit post completion of the safety follow-up in the study (Week 29) based on the investigator's discretion.

Immunogenicity results

Three (4.3%) patients in DRL_RI group were ADA positive at baseline (pre-dose); all tested ADA- negative after dosing and none were NAb positive. Post dosing with DRL_RI, 1 (1.4%) new patient tested ADA positive on Day 15, Week 8, and Week 12, was also NAb positive at Week 8 but later tested NAb negative at Week 12. Titres

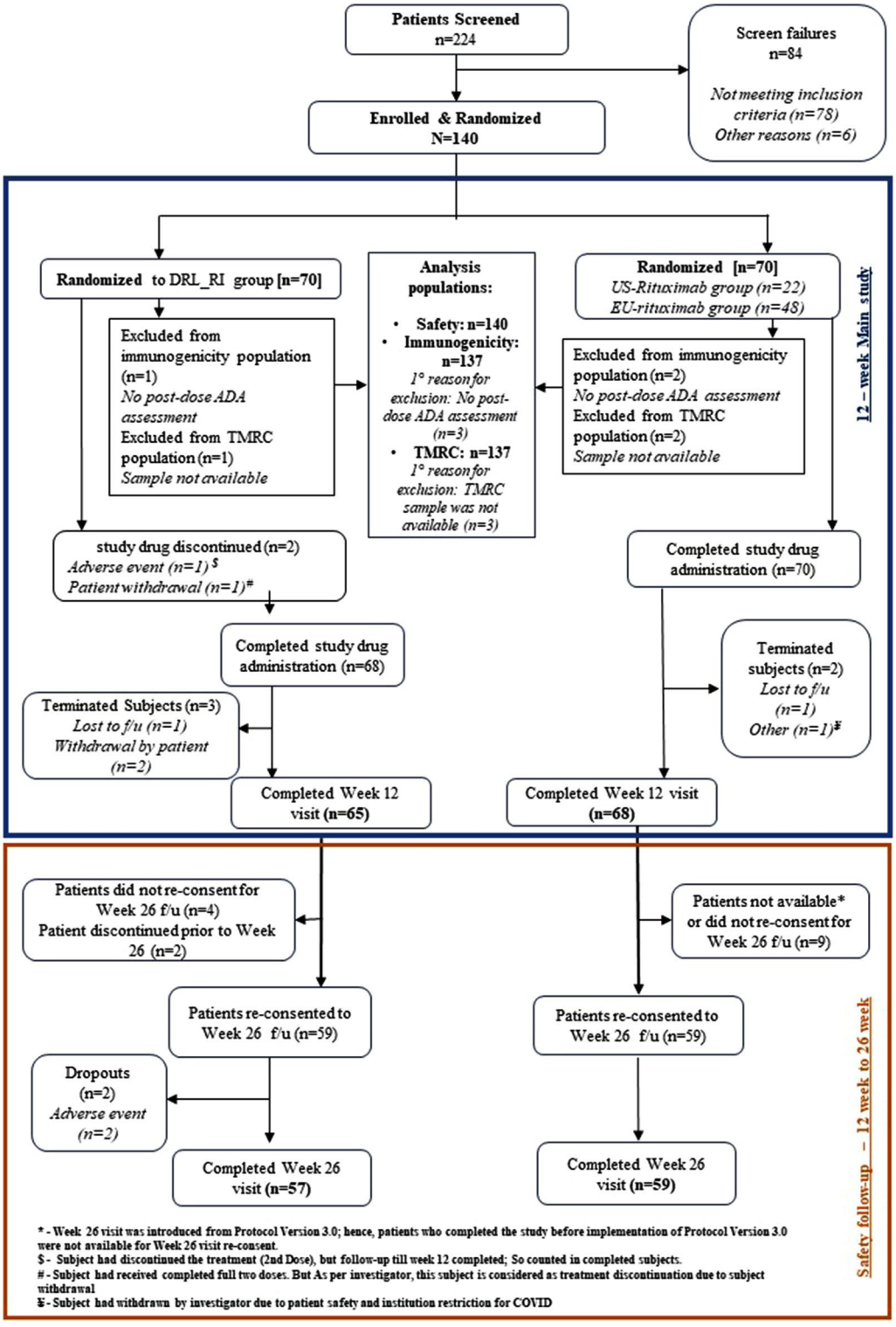

Fig. 2 CONSORT Flow Chart for Patient Disposition. Abbreviations: ADA, anti-drug antibody; DRL_RI, biosimilar rituximab; f/u, follow-up; N/n, number of patients; TMRC, time-matched rituximab concentration

Table 1 Baseline demographics and Disease characteristics (all enrolled patients)

Characteristic	DRL_RI (*N* = 70)	RP/RMP (*N* = 70)	Total (*N* = 140)
Age, years			
Mean (SD)	59.5 (11.7)	60.1 (11.8)	59.8 (11.7)
Min, Max	34, 85	24, 86	24, 86
Gender, n (%)			
Male	16 (22.9)	9 (12.9)	25 (17.9)
Female	54 (77.1)	61 (87.1)	115 (82.1)
Race, n (%)			
White	69 (98.6)	70 (100)	139 (99.3)
Black or African American	1 (1.4)	0	1 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	7 (10.0)	5 (7.1)	12 (8.6)
Not Hispanic or Latino	60 (85.7)	64 (91.4)	124 (88.6)
Unknown	3 (4.3)	1 (1.4)	4 (2.9)
Baseline BMI, kg/m^2			
Mean (SD)	28.3 (5.5)	27.2 (6.8)	27.8 (6.2)
Min, Max	19.1, 45.7	17.5, 52.0	17.5, 52.0
Source of rituximab drug in prior exposure			
RP: Reference Product [US-rituximab]	23 (32.9)	22 (31.4)	45 (32.1)
RMP: Reference Medicinal Product [EU-rituximab]	47 (67.1)	48 (68.6)	95 (67.9)
Duration of RA at randomization, Months Mean (SD)	134.6 (69.5)	104.4 (52.7)	120.6 (63.1)
Time from prior rituximab treatment, Months Mean (SD)	7.5 (2.7)	7.6 (2.9)	7.6 (2.8)
Patients with prior treatment course(s) with rituximab, n (%)			
1	21 (30.0)	26 (37.1)	47 (33.6)
> 1	49 (70.0)	44 (62.9)	93 (66.4)

Abbreviations: BMI: body mass index; EU: European Union; EU-rituximab: European Union approved rituximab (MabThera®); Max: maximum; Min: minimum; RA: rheumatoid arthritis; SD: standard deviation; US: United States; US-rituximab: United States licensed rituximab (Rituxan®)

Note: Percentages are based on the number of patients in the safety population

BMI was calculated as (body weight in kilograms)/(height in meters)^2

Duration of RA at randomization (Months) = (date of randomization - date of first diagnosis)/30.4375

Time from prior rituximab treatment (Months) = (date of randomization - date of last RA treatment date)/30.4375

for these ADA-positive patients decreased by the end of the study (Table 2). One (1.5%) patient in RP/RMP group tested ADA positive at baseline (pre-dose). This patient and another patient tested ADA positive at Week 12; none of these two patients were NAb positive till Week 12, though the titres did not decrease in these patients. Overall, ADA and NAb incidences were comparable with

Table 2 Summary of Antidrug Antibody Evaluations in study patients (Immunogenicity Population)

Visit	DRL_RI (*N* = 69)	RP/RMP (*N* = 68)	Total (*N* = 137)
Baseline			
ADA Positive, *n (%)*	3 (4.3)	1 (1.5)	4 (2.9)
NAb Positive, *n (%)*	0	0	0
Titre: *Median [Q1, Q3]*	360 [180, 720]	360 [360, 360]	360 [270, 540]
Day 15			
ADA Positive, *n (%)*	1 (1.4)	0	1 (0.7)
NAb Positive, *n (%)*	0	0	0
Titre: *Median [Q1, Q3]*	180 [180, 180]	-	180 [180, 180]
Week 4			
ADA Positive, *n (%)*	0	0	0
NAb Positive, *n (%)*	0	0	0
Titre: *Median [Q1, Q3]*	0	0	0
Week 8			
ADA Positive, *n (%)*	1 (1.4)	0	1 (0.7)
NAb Positive, *n (%)*	1 (1.4)	0	1 (0.7)
Titre: *Median [Q1, Q3]*	1440 [1440, 1440]	-	1440 [1440, 1440]
Week 12 (end of study)			
ADA Positive, *n (%)*	1 (1.4)	2 (2.9)	3 (2.2)
NAb Positive, *n (%)*	0	0	0
Titre: *Median [Q1, Q3]*	720 [720, 720]	540 [360, 720]	720 [360, 720]

Abbreviations: ADA: anti-drug antibody; EU-rituximab: European Union approved rituximab (MabThera®); Nab: neutralizing antibody; Q1: first quartile; Q3: third quartile; US-rituximab: United States licensed rituximab (Rituxan®)

no significant differences in the ADA titres between the two groups in the study (Table 2).

Time-matched rituximab concentration (TMRC)

Median TMRC values were comparable between the groups: 88.63 µg/mL in DRL_RI group and 100.8 µg/mL in RP/RMP group on Day 15. Week 4 showed the highest median TMRC: 141.2 µg/mL for DRL_RI vs. 159.4 µg/mL for RP/RMP. At Week 8, the median TMRC declined to 49.1 µg/mL and 69.9 µg/mL, respectively, and further to 20.3 µg/mL and 29.9 µg/mL, respectively, at Week 12. Blood levels in the treatment arms were comparable and did not show interference in the detection of immunogenicity.

Safety results

TEAE incidence was comparable between DRL_RI (34.3%) and RP/RMP groups (38.6%). Overall, the incidences of drug-related TEAEs, TEAEs leading to treatment discontinuation, Grade≥3 TEAEs, and treatment-emergent SAEs were not different between the groups. Two (2.9%) patients in DRL_RI group reported drug- related IRR Grade 1—itching in the throat and

roof of the mouth in 1 patient, and nausea after infusion in other patient—none were serious nor led to any treatment discontinuation. No anaphylactic reactions were reported (Table 3).

Common TEAEs in RP/RMP vs. DRL_RI group included infections and infestations (18.6% vs. 8.6%), gastrointestinal disorders (8.6% vs. 4.3%), nervous system disorders (8.6% vs. 1.4%), and musculoskeletal and connective tissue disorders (4.3% vs. 2.9%). Common adverse events (>3%) in RP/RMP group included diarrhoea and headache (7.1% of patients, each) and COVID-19 and nasopharyngitis (4.3% of patients, each); no AEs were reported in >3% frequency in DRL_RI group.

Drug-related TEAEs included IRRs (2.9%) and diarrhoea (1.4%) in DRL_RI group (overall 4.3%), while dizziness, embolic stroke, headache, bronchitis, pharyngitis, hypersensitivity, and rash, each in 1.4% patients in RP/RMP group (overall 5.7%). Grade 3 TEAEs in DRL_RI group included COVID-19 pneumonia, myocardial infarction, and bile duct stone in 1 patient each. Grade 4 TEAE of fungal infection and a Grade 5 TEAE of COVID-19 pneumonia, both, were reported in 1 patient; Grade 5 COVID-19 event was fatal. Grade 3 TEAEs reported in RP/RMP group were cystitis in 1 patient; and empyema, septic shock, enteritis, and embolic stroke in 1 patient. No Grade 4 or Grade 5 TEAE was reported in RP/RMP group.

Four (5.7%) patients in DRL_RI group and 2 (2.9%) patients in RP/RMP group experienced an SAE. Treatment-emergent SAEs in DRL_RI group included COVID-19 pneumonia in 2 patients resulting in death of 1 patient, myocardial infarction and intestinal resection in 1 patient, each; none of these were related to DRL_RI. Treatment-emergent SAEs in RP/RMP group included enteritis, cystitis, empyema, septic shock, and embolic stroke, each in 1 (1.4%) patient; of these, embolic stroke was related to RP/RMP.

DRL_RI was discontinued in 1 patient due to Grade 2 drug hypersensitivity (to amlodipine), not related to DRL_RI; while RP/RMP was discontinued in 1 patient due to Grade 2 hypersensitivity considered related to rituximab. The incidence of EOSI (COVID-19 and related) was not relevantly different between DRL_RI (3 patients) and RP/RMP groups (4 patients). In DRL_RI group, 1 patient had Grade 2 COVID-19, and 2 patients had serious COVID-19 pneumonia (Grade 3 and Grade 5-fatal). In RP/RMP group, 1 patient had Grade 2 COVID-19 pneumonia and 3 patients had Grade 2 COVID-19, which resolved during the study.

Table 3 Summary of adverse events (Safety Population)

Description	DRL_RI (*N* = 70) *n* (%) (e)	RP/RMP (*N* = 70) *n* (%) (e)	Total (*N* = 140) *n* (%) (e)
All Adverse event	25 (35.7) (37)	27 (38.6) (54)	52 (37.1) (91)
TEAEs	24 (34.3) (35)	27 (38.6) (54)	51 (36.4) (89)
Study drug-related TEAEs	3 (4.3) (3)	4 (5.7) (7)	7 (5.0) (10)
TEAEs leading to treatment discontinuation	1 (1.4) (1)[a]	1 (1.4) (1)	2 (1.4) (2)
TEAEs leading to death	1 (1.4) (1)	0	1 (0.7) (1)
Study drug-related TEAEs leading to death	0	0	0
TEAEs of Grade 3 or higher	4 (5.7) (5)	2 (2.9) (5)	6 (4.3) (10)
Treatment-emergent SAE	4 (5.7) (4)	2 (2.9) (5)	6 (4.3) (9)
Treatment-emergent study drug-related SAE	0	1 (1.4) (1)	1 (0.7) (1)
Treatment-emergent SAE leading to treatment discontinuation	0	0	0
Hypersensitivity reactions	0	1 (1.4) (1)	1 (0.7) (1)
TEAEs leading to treatment discontinuation	0	1 (1.4) (1)	1 (0.7) (1)
Infusion-related reactions	2 (2.9) (2)	0	2 (1.4) (2)
Anaphylactic reactions	0	0	0
TEAEs occurring in > 3% of patients			
Infections and infestations	6 (8.6) (7)	13 (18.6) (19)	19 (13.6) (26)
COVID-19	1 (1.4) (1)	3 (4.3) (3)	4 (2.9) (4)
Nasopharyngitis	0	3 (4.3) (3)	3 (2.1) (3)
Gastrointestinal disorders	3 (4.3) (3)	6 (8.6) (9)	9 (6.4) (12)
Diarrhoea	2 (2.9) (2)	5 (7.1) (6)	7 (5.0) (8)
Nervous system disorders	1 (1.4) (1)	6 (8.6) (8)	7 (5.0) (9)
Headache	0	5 (7.1) (5)	5 (3.6) (5)

Abbreviations: EU-rituximab, European Union approved rituximab (MabThera®); TEAE, treatment-emergent adverse event; SAE, serious adverse event; USrituximab, United States licensed rituximab (Rituxan®)

[a] Patient had reported Grade 2 drug hypersensitivity (to amlodipine), leading to treatment discontinuation

Note: The number of patients is represented by n. Each patient was counted only once if the patient reported 1 or more events, the number of events is represented as (e) and could include multiple events for a patient. Percentages are based on the number of patients in the safety population

Discussion

The US FDA guidance [10] requires biosimilar developers to evaluate effects of a single cross-over from the reference product to the proposed biosimilar in terms of hypersensitivity, immunogenicity, or other reactions. This study was conducted to fulfil this regulatory agency requirement. This study demonstrated that the incidences of ADA and Nab, and ADA titres were comparable for patients who transitioned to DRL_RI from RP/RMP versus those who continued with RP/RMP; TEAE incidences were also comparable between the groups.

Overall, these findings are similar to those reported for studies for rituximab and other bDMARDs upon transition to their respective biosimilars. Switching was reported with no loss of efficacy, and without any increase in adverse events or immunogenicity [11, 12].

Particularly, switching from reference rituximab to other approved biosimilar rituximab – PF-05280586 [13], CT-P10 [14], GP2013 [15], and ABP 798 [16] – have demonstrated comparable efficacy and no increased concerns of safety or immunogenicity post switching.

For a biosimilar product, immunogenicity is an important consideration alongside efficacy and safety. ADA incidences up to 12 weeks after dosing was low in both groups: 1.4% in DRL_RI vs. 2.9% in RP/RMP. Only 1 (1.4%) DRL_RI patient was NAb positive at Week 8. Furthermore, similar TMRC values throughout stipulated timepoints are supportive of no expected drug level differences between the treatments, and no interference in immunogenicity evaluation owing to differences in circulating rituximab concentrations. In our study, the post-transition ADA data is lower than the published ADA incidence of 11 – 12.7% with reference rituximab [6, 7], and comparable to data for other rituximab biosimilars switching in RA [13, 14]. In PF- 05280586 extension study, patients with active RA were offered up to 3 additional courses of treatment, with or without a single transition from RP/RMP to PF-05280586. The ADA incidence with the combined courses was 13.3% with anti-rituximab antibody assay and 10.0% with anti–PF-05280586 antibody assay [13]. The phase 3 extension study of CT-P10 reported an ADA incidence of 4.1%, 3.1%, 12.9% and 6.4%, respectively, in patients maintained on CT-P10 or RP, or after a single switch from either RP/RMP to CT-P10. Nab was detected in 1(0.8%) patient maintained on CT-P10 [14]. In a randomized clinical trial, switching to GP2013 from rituximab was associated with no ADA incidence. Only 1 patient on reference rituximab developed ADA; no NAbs were observed following the switch [15]. A single transition from RP to ABP 798 did not impact immunogenicity: 14.4% in ABP 798 group, 13.8% in RMP group, and 20.6% in the RP switching to ABP 795 group reported binding ADAs; majority of ADA results were transient. Of these, NAbs were reported in 8.2%, 4.3%, and 10.3% patients, respectively [16]. Overall, the ADA incidences, titres, and neutralizing capacity from our study suggest comparable immunogenicity between DRL_RI and reference rituximab upon transition; and is in line with similar reported literature for other rituximab biosimilars.

Monitoring of IRR is an important recommendation for patients on reference rituximab transitioning to a biosimilar [12]. IRRs observed with transition in this study are lower than reported IRRs incidences of 23–27% following the first infusion and 9% after the second infusion of rituximab [6, 7]. In this study, 2.9% DRL_RI patients reported IRRs; none were serious nor required treatment discontinuation. Grade>3 events were reported in 5.7% and 2.9% patients from DRL_RI and RP/RMP groups, respectively. Only 2 patients discontinued treatment — 1 in DRL_RI group due to drug hypersensitivity (to amlodipine) not related to DRL_RI, and 1 in RP/RMP group due to hypersensitivity related to rituximab. Common AEs in this study – infections and infestations (13.6%), gastrointestinal disorders (6.4%), nervous system disorders (5.0%), and musculoskeletal and connective tissue disorders (3.6%) – are expected findings for rituximab; RP/RMP group had a higher incidence. Incidences of infection-related AEs was lower in both groups in this transition study as compared to reports from pivotal rituximab trials [17–20], as well as the comparative study of DRL_RI with rituximab [8]. SAEs were lower (5.7% DRL_RI vs. 2.9% RP/RMP) and comparable across groups, and the event profile was consistent with the reported literature on rituximab use in RA [17–20]. Further, the IRR and safety profile observed with DRL_RI in this study are similar to the data reported from switching studies of other rituximab biosimilars. Patients switching to GP2013 or continuing treatment with rituximab showed hypersensitivity incidences of 9.4% and 11.1%, and IRRs of 11.3% and 18.5%, respectively [15]. A low IRR rate (6 of 185 patients), 11.6% of ≥Grade 3 TEAEs, and no apparent relationship between IRRs and ADA was reported with or without single transition from RP/RMP to PF-05280586 [13]. For patients maintained on CT-P10 or RP, or after a single switch from either RP/RMP to CT-P10 reported a similar rate– 4% for IRRs as well as ≥Grade 3 TEAEs across groups [14]. IRRs including hypersensitivity were reported in 15.5% patients vs. 15.4% patients in ABP 798 and 8.7% patients in RMP groups. The incidences of all grade TEAEs (54.4%), grade≥3 AEs (8.7%), SAEs (7.8%) in the patients with single transition was comparable across other groups [16]. Overall, the safety findings from this study are in line with the reports for other rituximab biosimilars, and the known safety profile of rituximab [6, 7], suggestive of no new safety concerns in patients transitioning to DRL_RI.

This study has following limitation: The study was not statistically powered to detect differences in the endpoints between the two treatment groups. The study sample size was estimated without a formal statistical hypothesis. As a result, descriptive analysis has been presented. A key outcome of the study was that it further strengthened the totality of evidence for biosimilarity demonstration of DRL_RI with both, RP and RMP (pooled), providing a robust reference group.

Despite being an established treatment option for RA patients, access to original biologics like rituximab can be highly limited for patients, particularly from developing countries. Biosimilar can not only boost accessibility but also provide a cost-effective option; hence findings from such studies provide valuable evidence for treating physicians in clinical decision-making while considering switching from reference rituximab to DRL_RI.

Conclusion

This study in RA patients demonstrated that a single transition from RP/RMP to DRL_RI did not have any impact on safety and immunogenicity. The incidence of ADA response and overall safety was consistent with the published data for rituximab.

Abbreviations

ADAs	Anti-Drug Antibodies
AE	Adverse Event
bDMARDs	Biologic Disease-Modifying Anti-Rheumatic Drugs
CD	Cluster of Differentiation
cDMARDs	Conventional Disease-Modifying Anti-Rheumatic Drugs
DRL	Dr. Reddy's Laboratories S.A
DRL_RI	DRL's proposed Rituximab biosimilar
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medical Agency
EOSI	Event Of Special Interest
EU	European Union
IgG1	Immunoglobulin G1
IRRs	Infusion-Related Reactions
JAK	Janus Kinase
LTBFL	Low Tumour Burden Follicular Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAbs	Neutralizing Antibodies
PD	Pharmacodynamic
PK	Pharmacokinetic
RA	Rheumatoid Arthritis
RMP	Reference Medicinal Product
RP	Reference Product
SAEs	Serious Adverse Events
SD	Standard Deviation
TMRC	Time-Matched Rituximab Concentration
TEAEs	Treatment-Emergent Adverse Events
US	United States
US FDA	US Food and Drug administration

Supplementary Information

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Supplementary Material 1: Patient Eligibility Criteria.

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Author contributions

All the authors have provided substantial contributions to the conception or design of the work, the acquisition of the data, and the interpretation of data. PR performed the statistical analysis, and DU, NR, PR, and NM contributed to the analysis interpretation. AB, DI, NS, AB and LAH contributed to the acquisition of data. DU and NM wrote the first draft. All the authors participated in the final drafting of the work or revising it critically for important intellectual content. All authors contributed to the final approval of the version published.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was reviewed and approved by the respective regulatory agencies, and ethics committees at each participating centre. All participating patients provided written informed consent prior to entering the study and before initiation of any study-related procedure.

Consent for publication

Not applicable.

Competing interests

DU, NR, PR, and NM are current employers of Dr.Reddy's Laboratories Ltd.,

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