Pharmacokinetic Similarity and Comparative Pharmacodynamics, Safety, Efficacy, and Immunogenicity of DRL_RI With Reference Rituximab in Biologics-Naïve Patients With Moderate-to-Severe Rheumatoid Arthritis: A Double-blind, Randomized, 3-arm Study

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Detailed List Exclusion Criteria

Table S1 Exclusion Criteria

- Prior therapy with alkylating agents or azathioprine; other biologics including rituximab and biologic disease modifying anti-rheumatic drugs (DMARDs); or leflunomide therapy within 3 months of screening
- Patients receiving double/triple DMARDs with azathioprine, Leflunomide, or any agent requiring more than 4 weeks washout
- Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
- Patients who have had any therapy with intra-articular injections (e.g. corticoids) required for a flare up and up to 4 weeks prior to screening
- Any investigational drug within 30 days or 5 times half-life, whichever was longer, prior to screening
- Patients requiring vaccination or who were vaccinated at least 4 weeks prior to administration of the study drugs
- Patients with underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious, or gastrointestinal conditions, which in the opinion of the Investigator immunocompromised the patient
- Infection requiring hospitalization, parenteral, antimicrobial therapy, or judged clinically significant by the Investigator within 3 months prior to first dose of study drug
- Patients with history of or current clinical fibromyalgia or juvenile idiopathic arthritis
- Patients with secondary Sjogren's syndrome
- Patients with the laboratory abnormalities in white blood cells, platelets, neutrophils, hemoglobin; serum IgG, IgM, IgA below lower limit of normal (LLN); abnormal liver and renal function tests and any clinically relevant abnormality detected on screening history, physical examination, clinical laboratory, chest X-ray, or electrocardiogram (ECG)
- Patients with systemic manifestations of rheumatoid arthritis (RA) and RA patients with Functional Status Class IV classified according to the ACR 1991 revised criteria
- Patients with other inflammatory diseases which might confound the evaluation of the efficacy (e.g. Crohn's disease, ulcerative colitis)
- Any current illness requiring antibiotics, or symptoms of a resolving illness, within 2 weeks prior to screening
- Patients with evidence of active, suspected, or inadequately treated tuberculosis, positive serological test for hepatitis B or C or HIV
- History of cardiovascular disease with New York Heart Association Functional Class II or significant cardiac disease arrhythmias, or history of stroke, or uncontrolled hypertension (systolic blood pressure [BP] $\geq$ 160 mmHg and diastolic BP $\geq$ 95 mmHg)
- History of lymphoproliferative disease, or organ allograft
- History of cancer
- History of allergy or hypersensitivity to any of the compounds used in the study
- Patients who lost or donated $\geq$ 400 mL blood in the 8 weeks prior to randomization
- Pregnant or lactating women, or women planning to become pregnant during the study
- Any condition that prevented compliance, such as history of chronic alcohol or drug abuse, significant mental or nervous disorder or other illness that would, in the Investigators opinion, interfere with compliance with the study requirements or be detrimental to patient safety

Abbreviations:
BP: blood pressure
DMARDs disease modifying anti-rheumatic drugs
HIV Human immunodeficiency virus
LLN Lower limit of normal
mL: milliliter
RA: rheumatoid arthritis

Sampling Schedule

Table S2 Pharmacokinetic Sampling Schedule for Rituximab Infusion

Infusion	Time Point†
Infusion 1	Pre-infusion
	3 hours after starting infusion)
	End of infusion
	1 hour after end of infusion
	6 hour after end of infusion
	Day 2
	Day 3
	Day 8
Infusion 2*	Pre-infusion
	3 hours after starting infusion
	End of infusion
	1 hour after end of infusion
	6 hour after end of infusion
	Day 2
	Day 3
	Day 8
	Day 15
	Week 4
	Week 6
	Week 8
	Week 10
	Week 14

*Day 15 after first infusion
† Time points are relative to infusion

Table S3 Sampling Schedule for CD 19+ Cell Recovery

Infusion	Time Point†
Infusion 1	Pre-infusion
	3 hours after starting infusion
	End of infusion
	6 hour after end of infusion
	Day 2
Infusion 2*	Pre-infusion
	6 hour after end of infusion
	Day 2
	Day 15
	Week 6
	Week 10
	Week 14
	Week 18
	Week 22

*Day 15 after first infusion
† Time points are relative to infusion

Treatment Compliance

Table S4 Summary of Rituximab Treatment Compliance (Safety Analysis Population)

Compliance	DRL_RI (N = 91)	RTX-US (N = 92)	RTX-EU (N =93)	Total (N = 276)
≤ 25%, n (%)	0	3 (3.3)	1 (1.1)	4 (1.4)
> 75%, n (%)	91 (100.0)	89 (96.7)	92 (98.9)	272 (98.6)
≥ 95%, n (%)	91 (100.0)	89 (96.7)	92 (98.9)	272 (98.6)

Abbreviations: RTX-EU = MabThera®; RTX-US = Rituxan®.
Percentages are based on number of patients within each treatment group under Safety Analysis Population (N).
Total volume infused are categorized.

Analysis Population

Table S5 Patient Analysis Population

Category	DRL_RI (N=91) n (%)	RTX-US (N=92) n (%)	RTX-EU (N=93) n (%)	Total (N=276) n (%)
ITT Population-Efficacy[a]	88 (96.7)	87 (94.6)	87 (93.5)	262 (94.9)
Per-Protocol Population-Efficacy	82 (90.1)	81 (88.0)	79 (84.9)	242 (87.7)
Per-Protocol Population (ACR)	82 (90.1)	81 (88.0)	79 (84.9)	242 (87.7)
Per-Protocol Population (DAS28 –CRP)	81 (89.0)	81 (88.0)	79 (84.9)	241 (87.3)
Per-Protocol Population (HAQ-DI)	82 (90.1)	81 (88.0)	79 (84.9)	242 (87.7)
Safety Analysis Population	91 (100)	92 (100)	93 (100)	276 (100)
PK Population(excluding ADA-positive)[b]	79 (86.8)	73 (79.3)	78 (83.9)	230 (83.3)
PK Population Sensitivity Analysis 1[c]	88 (96.7)	87 (94.6)	85 (91.4)	260 (94.2)
PK Population Sensitivity Analysis 2[d]	73 (80.2)	72 (78.3)	75 (80.6)	220 (79.7)
PD Population for DAS28 – CRP	86 (94.5)	86 (93.5)	85 (91.4)	257 (93.1)
PD Population for B-cell analysis	86 (94.5)	87 (94.6)	86 (92.5)	259 (93.8)

Abbreviations: ACR = American College of Rheumatology; ADA = Anti-drug antibody; CRP = C-reactive protein; DAS = Disease activity score; HAQ-DI = Health Assessment Questionnaire Disability Index; ITT = intent-to-treat; LOCF = Last observation carried forward; PD = Pharmacodynamic; PK = Pharmacokinetic; PP = per-protocol; RTX-EU = MabThera®; RTX-US = Rituxan®.

Percentages were based on the number of randomized patients in the study (N).

[a]All patients in the ITT Population were included in the PP Population, except for those patients excluded because of major protocol deviations having significant impact on the patient safety, data integrity, and efficacy endpoints.

[b]Patients with major protocol deviations (e.g. incomplete study drug administration, missed samples for critical time points, or with confirmed antibodies to study drug) were not included in the PK Population.

[c]Sensitivity Analysis 1 PK Population: This population includes all patients having confirmed ADA positive results and patients only randomized between the two products available at the site at the time

[d]Sensitivity Analysis 2 PK Population: This population excludes both patients only randomized between the two products available at the site at the time and patients having confirmed ADA positive results.

Prior, Concomitant, and Pre-medication

Table S6 Summary of Rheumatoid Arthritis Medications-(Safety Analysis Population) Analysis Population

ATC Level 1 ATC Level 3 Preferred term	DRL_RI (N=91) n (%)	RTX-US (N=92) n (%)	RTX-EU (N=93) n (%)	Total (N=276) n (%)
Number of patients with at least 1 medication reported	**91 (100)**	**92 (100)**	**93 (100)**	**276 (100)**
Antineoplastic and Immunomodulating agents	91 (100)	92 (100)	93 (100)	276 (100)
Antimetabolites	91 (100)	92 (100)	93 (100)	276 (100)
Methotrexate	90 (98.9)	91 (98.9)	93 (100)	274 (99.3)
Methotrexate sodium	2 (2.2)	1 (1.1)	1 (1.1)	4 (1.4)
Immunosuppressants	7 (7.7)	6 (6.5)	3 (3.2)	16 (5.8)
Leflunomide	6 (6.6)	6 (6.5)	3 (3.2)	15 (5.4)
Hydroxychloroquine	1 (1.1)	0	0	1 (0.4)
Musculo-skeletal system	52 (57.1)	54 (58.7)	60 (64.5)	166 (60.1)
Anti-inflammatory and anti-rheumatic products, non-steroidal	52 (57.1)	54 (58.7)	60 (64.5)	166 (60.1)
Hydroxychloroquine	35 (38.5)	28 (30.4)	29 (31.2)	92 (33.3)
Hydroxychloroquine sulfate	17 (18.7)	20 (21.7)	21 (22.6)	58 (21.0)
Sulfasalazine	4 (4.4)	4 (4.3)	5 (5.4)	13 (4.7)
Nimesulide	0	2 (2.2)	4 (4.3)	6 (2.2)
Algiril	2 (2.2)	2 (2.2)	1 (1.1)	5 (1.8)
Aiacerein	1 (1.1)	1 (1.1)	0	2 (0.7)
Glucosamin sulfate/msm	1 (1.1)	0	1 (1.1)	2 (0.7)
Glucosamine sulfate	1 (1.1)	1 (1.1)	0	2 (0.7)
Glucosamine	0	0	1 (1.1)	1 (0.4)
Joint ache dn	0	1 (1.1)	0	1 (0.4)
Methylsulfonylmethane	1 (1.1)	0	0	1 (0.4)
Rejoint	0	0	1 (1.1)	1 (0.4)
Anti-inflammatory/anti-rheumatic agents in combination	1 (1.1)	1 (1.1)	0	2 (0.7)
Enzoflam /03538601/	0	1 (1.1)	0	1 (0.4)
Moviz-3d	1 (1.1)	0	0	1 (0.4)
Systemic hormonal preparations, excl. sex hormones	19 (20.9)	9 (9.8)	10 (10.8)	38 (13.8)
Corticosteroids for systemic use, plain	19 (20.9)	9 (9.8)	10 (10.8)	38 (13.8)
Methylprednisolone acetate	14 (15.4)	6 (6.5)	4 (4.3)	24 (8.7)
Methylprednisolone	3 (3.3)	2 (2.2)	5 (5.4)	10 (3.6)
Prednisolone	2 (2.2)	1 (1.1)	0	3 (1.1)
Hydrocortisone	0	0	1 (1.1)	1 (0.4)
Alimentary tract and metabolism	13 (14.3)	11 (12.0)	10 (10.8)	34 (12.3)
Intestinal anti-inflammatory agents	13 (14.3)	11 (12.0)	10 (10.8)	34 (12.3)
Sulfasalazine	13 (14.3)	11 (12.0)	10 (10.8)	34 (12.3)

Abbreviations; ATC = Anatomical Therapeutic Chemical Classification; RTX-EU = MabThera®; RTX-US = Rituxan®.

Percentages are based on number of patients in each treatment group under Safety Analysis Population (N). Patients with multiple usage of the same medication within the same preferred term are counted only once.

PK Parameters in the Sensitivity analysis populations

Table S7 Summary of Key PK Parameters and its Comparison between Treatment Groups (PK Sensitivity Population 1 -including ADA-positive patients- N = 260)

Parameter (units)	Treatment	GLS Mean	Statistical Comparisons GLS Mean Ratio (91% CI) (%)		
			DRL_RI/ RTX-US	DRL_RI/ RTX-EU	RTX-US/ RTX-EU
PK Population – Primary Endpoints					
$AUC_{0\text{-}14\ days,\ first\ infusion}$ (µg.h/mL)	DRL_RI	39480	99.62 (93.86, 105.73)	95.11 (89.53, 101.05)	95.47 (89.88, 101.41)
	RTX-US	39630			
	RTX-EU	41510			
$AUC_{0\text{-}\infty,\ entire\ course}$ (µg·h/mL)	DRL_RI	142200	98.82 (91.43, 106.82)	93.14 (85.96, 100.93)	94.25 (87.00, 102.11)
	RTX-US	143900			
	RTX-EU	152700			
$AUC_{0\text{-}t,\ second\ infusion}$ (µg·h/mL)	DRL_RI	102000	99.31 (91.10, 108.27)	93.88 (86.01, 102.46)	94.53 (86.59, 103.20)
	RTX-US	102700			
	RTX-EU	108600			
PK Population – Secondary Endpoints					
$AUC_{0\text{-}t,\ entire\ course}$ (µg·h/mL)	DRL_RI	141500	99.12 (91.82, 106.99)	93.41 (86.35, 101.05)	94.25 (87.17, 101.90)
	RTX-US	142800			
	RTX-EU	151500			
$C_{max,\ first\ infusion}$ (µg/mL)	DRL_RI	330.958	103.88 (97.80, 110.33)	100.10 (94.15, 106.43)	96.36 (90.65, 102.44)
	RTX-US	318.600			
	RTX-EU	330.621			
$C_{max,\ second\ infusion}$ (µg/mL)	DRL_RI	408.550	101.73 (95.75, 108.07)	101.50 (95.46, 107.92)	99.78 (93.81, 106.13)
	RTX-US	401.621			
	RTX-EU	402.517			

Abbreviations: ANOVA = Analysis of variance; $AUC_{0\text{-}14\ days}$ = area under the plasma concentration–time curve from time 0 to day 14; $AUC_{0\text{-}t}$ = area under the plasma concentration–time curve from time 0 to last quantifiable concentration; $AUC_{0\text{-}\infty}$ = area under the plasma concentration–time curve from time 0 extrapolated to infinite time CI: Confidence interval; C_{max} = peak plasma concentration; GLS: Geometric least-squares; PK: Pharmacokinetic; RTX-EU = MabThera®; RTX-US = Rituxan®.

PK Sensitivity Population-1, N = 260 (DRL_RI, n = 88; RTX-US, n = 87; RTX-EU, n = 85).

The values are back transformed from the log scale.

Results based on an ANOVA model with treatment (DRL_RI, RTX-US and RTX-EU), ADA status, region, and gender being considered as fixed effects.

Table S8 Summary of Key PK Parameters and its Comparison between Treatment Groups (PK Sensitivity Population 2 –excluding ADA-positive and patients only randomized between the two products available at the site at the time -, N = 220)

Parameter (units)	Treatment	GLS Mean	Statistical Comparisons GLS Mean Ratio (91% CI) (%)		
			DRL_RI/ RTX-US	DRL_RI/ RTX-EU	RTX-US/ RTX-EU
PK Population – Primary Endpoints					
$AUC_{0\text{-}14\ days,\ first\ infusion}$ (µg.h/mL)	DRL_RI	44330	104.14 (98.14, 110.50)	98.94 (93.21, 105.03)	95.01 (89.56, 100.79)
	RTX-US	42570			
	RTX-EU	44810			
$AUC_{0\text{-}\infty,\ entire\ course}$ (µg.h/mL)	DRL_RI	168400	103.06 (94.71, 112.14)	96.24 (88.32, 104.87)	93.38 (85.76, 101.68)
	RTX-US	163400			
	RTX-EU	175000			
$AUC_{0\text{-}t,\ second\ infusion}$ (µg.h/mL)	DRL_RI	121500	103.69 (94.45, 113.83)	96.93 (88.29, 106.41)	93.48 (85.12, 102.66)
	RTX-US	117200			
	RTX-EU	125400			
PK Population – Secondary Endpoints					
$AUC_{0\text{-}t,\ entire\ course}$ (µg.h/mL)	DRL_RI	165700	103.00 (94.85, 111.86)	96.55 (88.78, 105.01)	93.74 (86.26, 101.86)
	RTX-US	160800			
	RTX-EU	171600			
$C_{max,\ first\ infusion}$ (µg/mL)	DRL_RI	361.421	108.41 (101.76, 115.50)	103.17 (96.80, 109.95)	95.16 (89.35, 101.36)
	RTX-US	333.380			
	RTX-EU	350.327			
$C_{max,\ second\ infusion}$ (µg/mL)	DRL_RI	437.014	107.79 (101.23, 114.78)	105.16 (98.76, 111.97)	97.56 (91.60, 103.91)
	RTX-US	405.430			
	RTX-EU	415.577			

Abbreviations: $AUC_{0\text{-}14\ days}$ = area under the plasma concentration–time curve from time 0 to day 14; $AUC_{0\text{-}t}$ = area under the plasma concentration–time curve from time 0 to last quantifiable concentration; $AUC_{0\text{-}\infty}$ = area under the plasma concentration–time curve from time 0 extrapolated to infinite time.
Abbreviations: CI: Confidence interval; C_{max} = peak plasma concentration; GLS: Geometric least-squares; PK: Pharmacokinetic; RTX-EU = MabThera®; RTX-US = Rituxan®.
PK Sensitivity Population-2, N = 260 (DRL_RI, n = 73; RTX-US, n = 72; RTX-EU, n = 75).
The values are back transformed from the log scale.
Results based on an ANOVA model with treatment (DRL_RI, RTX-US and RTX-US), region, and gender being considered as fixed effects.

Table S9 Proportion of Patients with B-cell Depletion (PD Population)

Visit	DRL_RI (N=86)	RTX-US (N=87)	RTX-EU (N=86)
20% Below the LLN			
48 hours Post Infusion 1, N evaluable	80	82	82
48 Hours Post Infusion 1,%	98.8	100	100
Difference (95% CI)		-1.3 (-6.75, 3.34)	-1.3 (-6.75, 3.34)
Week 16, N evaluable	78	81	79
Week 16, %	96.2	95.1	100
Difference (95% CI)		1.1 (-6.40, 8.61)	-3.8 (-10.71, 1.44)
Week 24, N evaluable	79	81	79
Week 24, %	67.1	69.1	78.5
Difference (95% CI)		-2.0 (-16.22, 12.19)	-11.4 (-24.73, 2.50)
Below the LOD			
48 hours Post Infusion 1, N evaluable	82	83	82
48 Hours Post Infusion 1, %	4.9	2.4	3.7
Difference (95% CI)		2.5 (-4.19, 9.69)	1.2 (-5.97, 8.62)
Week 16, N evaluable	80	82	79
Week 16, %	10.0	4.9	10.1
Difference (95% CI)		5.1 (-3.39, 14.13)	-0.1 (-10.00, 9.70)
Week 24, N evaluable	81	81	79
Week 24, %	0.0	3.7	1.3
Difference (95% CI)		-3.7 (-10.33, 1.44)	-1.3 (-6.83, 3.38)

Abbreviations: CI = Confidence intervalLOD = Limit of detection; LLN = Lower limit of normal; PD = Pharmacodynamic; RTX-EU = MabThera®; RTX-US = Rituxan®

B-cell depletion is defined as peripheral B-cell recovery to B-cell counts < LLN or LOD The LLN for B-cell counts in this study is 107.0 cells/μL.

N evaluable Patients with available data for the visit

Proportion (%) = (number of patients with depletion/number of evaluable patients for the visit)*100.

Difference (95% CI) = Difference in proportion of patients with depletion in DRL_RI group and RTX-US or RTX-EU.

Table S10 Mean DAS28-CRP values from Baseline to Week 24 (PP population)

	Mean ± SD values						
	Baseline	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
DRL-RI (N)	6.03 ± 0.68 (82)	5.03± 0.98 (82)	4.67 ± 1.04 (82)	4.41 ± 1.14 (80)	4.15 ± 1.12 (81)	4.08 ± 1.13 (81)	4.05 ± 1.11 (81)
RTX-US (N)	5.69 ± 0.77 (81)	4.81± 0.91 (80)	4.47 ± 0.96 (80)	4.25 ± 1.08 (80)	4.19 ± 1.07 (81)	4.02 ± 1.13 (80)	3.96 ± 1.12 (81)
RTX-EU (N)	5.75 ± 0.72 (79)	4.76 ± 1.01 (77)	4.33 ± 1.15 (77)	4.01 ± 1.17 (77)	3.90 ± 1.17 (79)	3.83 ± 1.12 (79)	3.82 ± 1.13 (79)

Abbreviations: DAS28-CRP = Disease activity score (28 joints) – C-reactive protein; RTX-EU = MabThera®; RTX-US = Rituxan®; SD = standard deviation

N = number of patients with available assessment in each treatment arm and visit under PP population.

Table S11 Incidence of Adverse Events Reported in ≥ 2% of Patients in any Treatment Group up to Week 24 (Safety Analysis Population)

SOC Preferred Term	DRL_RI (N = 91) n (%)	RTX-US (N = 92) n (%)	RTX-EU (N = 93) n (%)	Total (N =276) n (%)
Number of Patients with at least 1 AE	33 (36.3)	30 (32.6)	37 (39.8)	100 (36.2)
Infections and infestations				
Upper respiratory tract infection	4 (4.4)	3 (3.3)	5 (5.4)	12 (4.3)
Nasopharyngitis	2 (2.2)	4 (4.3)	1 (1.1)	7 (2.5)
Urinary tract infection	2 (2.2)	2 (2.2)	2 (2.2)	6 (2.2)
Gastrointestinal disorders				
Nausea	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.4)
Mouth ulceration	2 (2.2)	1 (1.1)	0	3 (1.1)
Abdominal pain upper	2 (2.2)	0	0	2 (0.7)
Investigations				
Alanine aminotransferase increased	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.4)
Aspartate aminotransferase increased	0	2 (2.2)	0	2 (0.7)
Musculoskeletal and connective tissue disorders				
Rheumatoid arthritis	3 (3.3)	1 (1.1)	2 (2.2)	6 (2.2)
Back Pain	0	0	2 (2.2)	2 (0.7)
General disorders and administration site conditions				
Pyrexia	2 (2.2)	4 (4.3)	3 (3.2)	9 (3.3)
Respiratory, thoracic and mediastinal disorders				
Cough	3 (3.3)	3 (3.3)	3 (3.2)	9 (3.3)
Throat irritation	0	2 (2.2)	1 (1.1)	3 (1.1)
Blood and lymphatic system disorders				
Anaemia	1 (1.1)	5 (5.4)	1 (1.1)	7 (2.5)
Neutropenia	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.4)
Eosinophilia	0	1 (1.1)	2 (2.2)	3 (1.1)
Skin and subcutaneous tissue disorders				
Pruritus	0	2 (2.2)	1 (1.1)	3 (1.1)
Rash	0	1 (1.1)	2 (2.2)	3 (1.1)
Injury, poisoning and procedural complications				
Infusion related reaction	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.4)
Nervous system disorders				
Headache	1 (1.1)	1 (1.1)	2 (2.2)	4 (1.4)
Vascular disorders				
Hypertension	1 (1.1)	0	2 (2.2)	3 (1.1)

Abbreviations: AE = Adverse event; RTX-EU = MabThera®; RTX-US = Rituxan®; SOC = System organ class.

SOC Preferred Term	DRL_RI (N = 91) n (%)	RTX-US (N = 92) n (%)	RTX-EU (N = 93) n (%)	Total (N =276) n (%)

Abbreviations: AE = Adverse event; RTX-EU = MabThera®; RTX-US = Rituxan®; SOC = System organ class.
Patients experiencing multiple events with the same preferred term were counted only once.
Percentages are based on number of patients within each treatment group under safety analysis population (N).

Table S12 Incidence of Adverse Events Reported in ≥ 2% of Patients in any Treatment Group up to Week 52 (Safety Analysis Population)

SOC Preferred Term	DRL_RI (N = 91) n (%)	RTX-US (N = 92) n (%)	RTX-EU (N = 93) n (%)	Total (N =276) n (%)
Number of Patients with at least 1 AE	27 (29.7)	28 (30.4)	29 (31.2)	84 (30.4)
Investigations				
B-lymphocyte count decreased	7 (7.7)	5 (5.4)	8 (8.6)	20 (7.2)
Alanine aminotransferase increased	0	2 (2.2)	1 (1.1)	3 (1.1)
Aspartate aminotransferase increased	0	2 (2.2)	1 (1.1)	3 (1.1)
Infections and infestations				
Upper respiratory tract infection	1 (1.1)	3 (3.3)	1 (1.1)	5 (1.8)
Body tinea	1 (1.1)	0	2 (2.2)	3 (1.1)
Musculoskeletal and connective tissue disorders				
Rheumatoid arthritis	3 (3.3)	1 (1.1)	4 (4.3)	8 (2.9)
Gastrointestinal disorders				
Mouth Ulceration	2 (2.2)	0	1 (1.1)	3 (1.1)
Respiratory, thoracic and mediastinal disorders				
Cough	0	2 (2.2)	4 (4.3)	6 (2.2)
General disorders and administration site conditions				
Pyrexia	3 (3.3)	1 (1.1)	2 (2.2)	6 (2.2)
Blood and lymphatic system disorders				
Anaemia	0	2 (2.2)	1 (1.1)	3 (1.1)
Vascular disorders				
Hypertension	1 (1.1)	0	2 (2.2)	3 (1.1)

Abbreviations: AE = Adverse event; RTX-EU = MabThera®; RTX-US = Rituxan®; SOC = System organ class.
Patients experiencing multiple events with the same preferred term were counted only once.
Percentages are based on number of patients within each treatment group under safety analysis population (N).

Table S13 Incidence of Serious Adverse Events up to Week 52 (Safety Analysis Population)

SOC Preferred Term	DRL_RI (N = 91) n (%)	RTX-US (N = 92) n (%)	RTX-EU (N = 93) n (%)	Total (N =276) n (%)
Number of patients with at least 1 SAE	3 (3.3)	5 (5.4)	10 (10.8)	18 (6.5)
Infections and infestations				
H1N1 influenza			1 (1.1)	1 (0.4)
Pneumonia	1 (1.1)			1 (0.4)
Urinary tract infection			1 (1.1)	1 (0.4)
Cellulitis			1 (1.1)	1 (0.4)
Gastroenteritis viral			1 (1.1)	1 (0.4)
Pyelonephritis acute			1 (1.1)	1 (0.4)
Injury, poisoning and procedural complications				
Femoral neck fracture			1 (1.1)	1 (0.4)
Forearm fracture			1 (1.1)	1 (0.4)
Humerus fracture		1 (1.1)		1 (0.4)
Infusion related reaction		1 (1.1)		1 (0.4)
Spinal cord compression fracture		1 (1.1)		1 (0.4)
Blood and lymphatic system disorders				
Febrile neutropenia		1 (1.1)		1 (0.4)
Neutropenia		1 (1.1)		1 (0.4)
Cardiac disorders				
Atrial fibrillation			1 (1.1)	1 (0.4)
Cardio-respiratory arrest			1 (1.1)	1 (0.4)
General disorders and administration site conditions				
Pyrexia			1 (1.1)	1 (0.4)
Sudden death	2 (2.2)			2 (2.2)
Gastrointestinal disorders				
Intestinal obstruction		1 (1.1)		1 (0.4)
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease			1 (1.1)	1 (0.4)
Musculoskeletal and connective tissue disorder				
Spondylolisthesis			1 (1.1)	1 (0.4)

Abbreviations: SAE = Serious adverse event; RTX-EU = MabThera®; RTX-US = Rituxan®; SOC = System organ class.
Patients experiencing multiple events with the same preferred term were counted only once.
Percentages are based on number of patients within each treatment group under safety analysis population (N).

Table S14 Proportion of Patients with B-cell Repletion (PD Population)

Visit	DRL_RI	RTX-US	RTX-EU
Above or equal to the LLN			
Week 24, N evaluable	81	81	79
Week 24, %	4.9	7.4	0
Difference (95% CI)		-2.5 (-10.85, 5.65)	4.9 (-0.59, 12.02)
Week 52, N evaluable	60	56	59
Week 52, %	33.3	23.2	23.7
Difference (95% CI)		10.1 (-6.31, 25.68)	9.6 (-6.59, 25.12)
Above or equal to 80% of baseline			
Week 24, N evaluable	81	78	78
Week 24, %	1.2	3.9	0
Difference (95% CI)		-2.6 (-9.55, 3.38)	1.2 (-3.57, 6.67)
Week 52, N evaluable	60	56	59
Week 52, %	21.7	14.3	6.8
Difference (95% CI)		7.4 (-6.91, 21.17)	14.9 (2.19, 27.53)

Abbreviations: LLN = Lower limit of normal; PD = Pharmacodynamic; RTX-EU = MabThera®; RTX-US = Rituxan®

B-cell repletion is defined as peripheral B-cell recovery to B-cell counts ≥ LLN or achievement of a B-cell counts at least 80% of the patient's baseline B-cell counts. The LLN for B-cell counts in this study is 107.0 cells/μL

N evaluable Patients with available data for the visit

Proportion (%) = (number of patients with repletion/number of evaluable patients for the visit)*100.

Difference (95% CI) = Difference in proportion of patients with depletion in DRL_RI group and RTX-US or RTX-EU.

Table S15 Summary of Other Secondary PK Parameters (Main PK Population, N = 230)

Parameter*	DRL_RI (N = 79)	RTX-US (N = 73)	RTX-EU (N = 78)
$T_{max,\ first\ infusion}$, median (minimum, maximum) (hours)	5.25 (3.00, 10.25)	5.25 (4.25, 10.33)	5.25 (3.00, 29.05)
$T_{max,\ second\ infusion}$, median (minimum, maximum) (hours)	5.25 (3.00, 10.33)	5.25 (3.08, 52.00)	5.25 (3.00, 27.25)
$t_{1/2;}$ (hours)	374 (30.1)	378 (25.0)	391 (23.9)
Cl (L/day)	0.254 (33.2)	0.254 (33.9)	0.238 (30.0)
Vz (L)	5.69 (26.3)	5.76 (23.1)	5.55 (26.4)

Abbreviations: Cl = total body clearance after second infusion; PK = Pharmacokinetic; RTX-EU = MabThera®; RTX-US = Rituxan®; $t_{1/2}$ = terminal elimination half-life after second infusion; T_{max} = time to peak plasma concentration; Vz = volume of distribution after second infusion.

*Values for secondary endpoints parameters are geometric means with geometric coefficient of variation expressed as a percent in parentheses except where indicated otherwise.

Table S16 ADA Titers up to Week 52 (PP Population)

	Median (minimum - maximum) ADA Titer				
	Baseline	**Week 4**	**Week 16**	**Week 24**	**Week 52**
DRL_RI (N=82)	1.0 (1 - 1)	NR	8.0 (8 - 8)	4.0 (1 - 8)	2.0 (1 - 2)
RTX-US (N=81)	NR	NR	1.0 (1 - 1)	1.0 (1 - 16)	2.0 (1 - 16)
RTX-EU (N=79)	NR	NR	8.0 (8 - 8)	9.0 (1 - 256)	1.0 (1 - 8)

Abbreviations: ADA = antidrug antibody; NR = not reported (as ADA titer values of less than 1); PP = per-protocol; RTX-US = Rituxan®; RTX-EU = MabThera®.

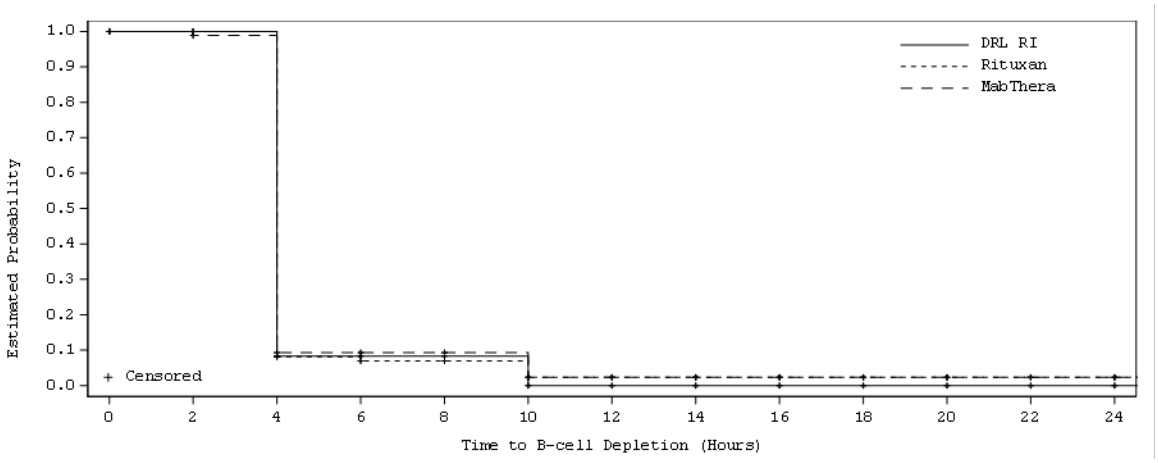

Fig S1 Kaplan-Meier Analysis of Time to B-cell Depletion (Below 20% of LLN) (PD Population)

Abbreviations: LLN = Lower limit of normal; PD = Pharmacodynamic; RTX-EU = Mabthera®; RTX-US = Rituxan®.
The confidence intervals are estimated based on the Kaplan-Meier estimation method. Patients who did not experience depletion are censored.

Peripheral blood B-cell recovery ≥ LLN or at least 80% of baseline B-cell Population

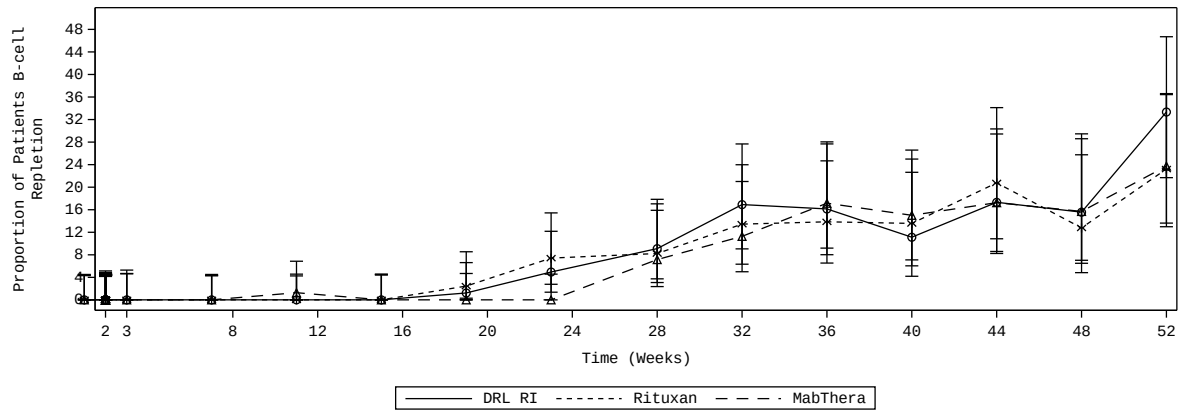

Fig S2a Proportion of Patients with B-cell Repletion Above or Equal to the Lower Limit of Normal

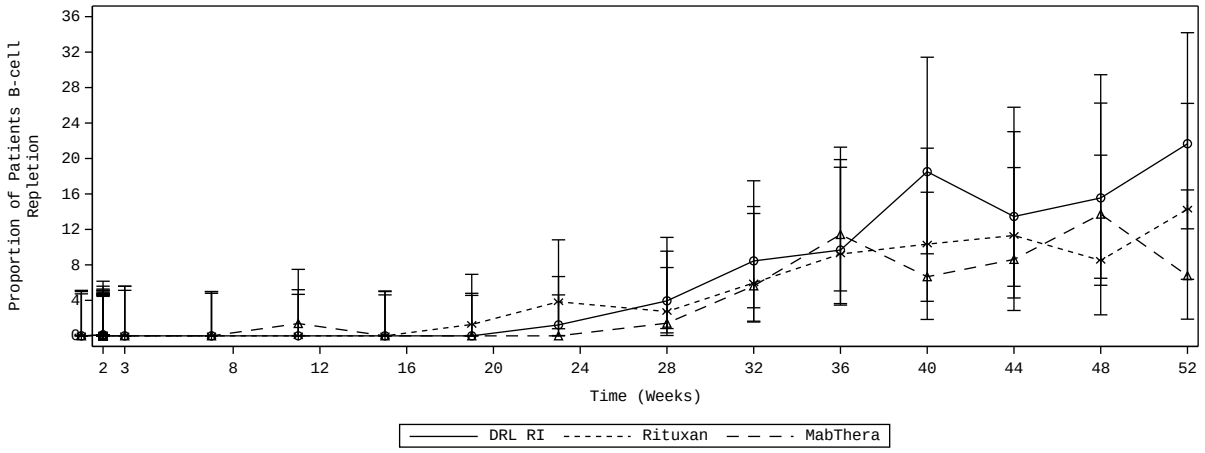

Fig S2b Proportion of Patients with B-cell Repletion Above or Equal to 80% of Baseline

Abbreviations: LLN = Lower limit of normal; RTX-EU = Mabthera®; RTX-US = Rituxan®.
B-cell repletion is defined as peripheral B-cell recovery to B-cell counts ≥ LLN B-cell count at least 80% of the patient's baseline B-cell counts. The LLN for B-cell counts in this study is 107.0 cells/µL.
Infusion 1-0 (h): week 0 Day 1 Pre-infusion; Infusion 2-0 (h): week 2 Day 1 pre-infusion, 3700 (h): week 22 respect to infusion 2, Week 24 respect to infusion 1
Upper and lower bounds indicated the 95% confidence interval.

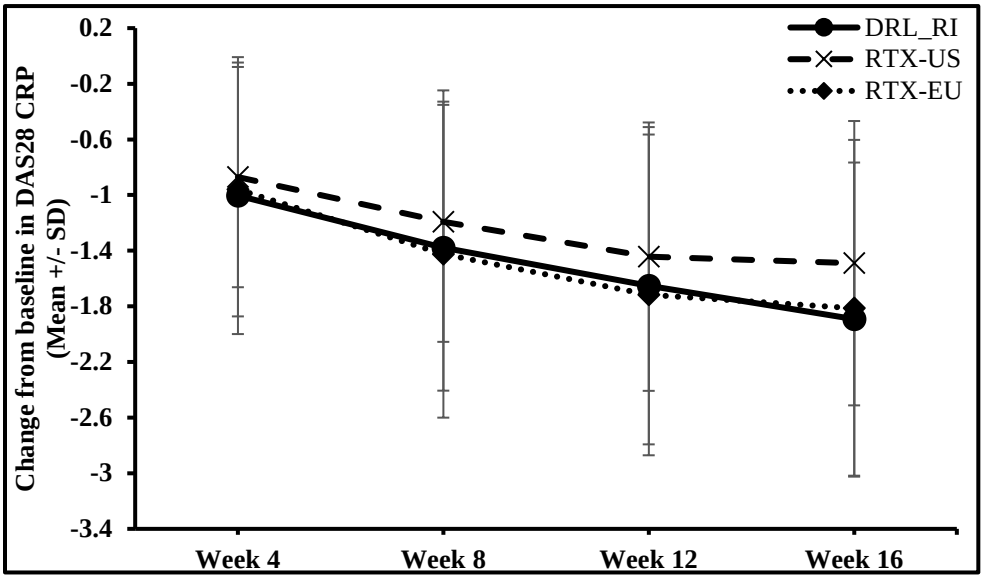

Figure S3 Change in Mean DAS28-CRP Score from Baseline up to Week 16 (PD population)

Abbreviations: DAS28-CRP = disease activity score (28 joints) - C-reactive protein; PD = pharmacodynamic; RTX-EU = MabThera®; RTX-US = Rituxan®; SD = standard deviation.
The geometric mean calculation for change from baseline columns are based on the ratio of visit value to baseline value.

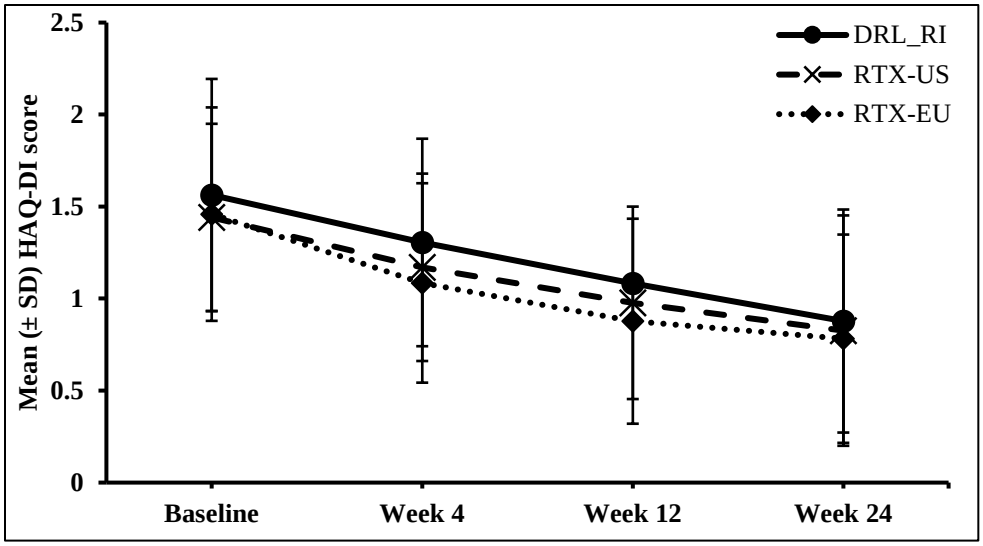

Figure S4 Mean HAQ-DI Score over 24 Weeks from Baseline (PP Population)

Abbreviations: HAQ-DI = Health Assessment Questionnaire Disability Index; PP = per-protocol; RTX-EU = MabThera®; RTX-US = Rituxan®; SD = standard deviation.
The geometric mean calculation for change from baseline columns is based on the ratio of visit value to baseline value.