A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects with Rheumatoid Arthritis to Biosimilar Rituximab (DRL_RI) or Continued Treatment with Rituxan® or MabThera®

NCT number: NCT04268771

Date of protocol : 10 July 2020

CLINICAL STUDY PROTOCOL

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EUDRACT: 2019-002810-37

A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects With Rheumatoid Arthritis to Biosimilar Rituximab (DRL_RI) or Continued Treatment With Rituxan® or MabThera®

PROTOCOL NO. RI-01-007

Sponsor:	Dr. Reddy's Laboratories S.A. Elisabethenanlage 11 CH-4051 Basel Switzerland
Sponsor Contact:	CI CI
Medical Lead:	CI
Version of Protocol:	Version 3.0, Amendment 2
Date of Protocol:	10 Jul 2020
Previous Date and Version	12 Aug 2019, Version 2.0 (Amendment 1)

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Dr. Reddy's Laboratories S.A. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Dr. Reddy's Laboratories S.A. The study will be conducted according to the International Council for Harmonisation Harmonised Tripartite Guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects With Rheumatoid Arthritis to Biosimilar Rituximab (DRL_RI) or Continued Treatment With Rituxan® or MabThera®
Protocol Number	RI-01-007
Protocol Date	10 Jul 2020

Protocol accepted and approved by:

CI

[redacted]

CI

[redacted]

Protocol Approval – Lead Statistician

Study Title A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects With Rheumatoid Arthritis to Biosimilar Rituximab (DRL_RI) or Continued Treatment With Rituxan® or MabThera®

Protocol Number RI-01-007

Protocol Date 10 Jul 2020

Protocol accepted and approved by:

CI [redacted]

CI [redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A randomized, double-blind, parallel group, multicenter study to assess the immunogenicity and safety of transitioning subjects with rheumatoid arthritis to biosimilar rituximab (DRL_RI) or continued treatment with Rituxan® or MabThera®" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, Amendment 2, dated 10 Jul 2020, the International Council for Harmonisation Harmonised Tripartite Guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Dr. Reddy's Laboratories S.A. or implement protocol changes without Independent Ethics Committee/Institutional Review Board approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Dr. Reddy's Laboratories S.A.

_____ _____

Signature of Principal Investigator Date

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Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	RI-01-007
Title:	A randomized, double-blind, parallel group, multicenter study to assess the immunogenicity and safety of transitioning subjects with rheumatoid arthritis to biosimilar rituximab (DRL_RI) or continued treatment with Rituxan® or MabThera®
Sponsor:	Dr. Reddy's Laboratories S.A. Elisabethenanlage 11 CH-4051 Basel Switzerland
Study Phase:	Phase 3 transition study
Study Sites:	It is planned that approximately 50 sites will be initiated for this study in up to 7 countries (including, but not restricted to, the United States [US]).
Indication:	Rheumatoid arthritis (RA)
Rationale:	The evaluation of pharmacokinetics (PK), efficacy, safety, and immunogenicity between a biosimilar and the innovator product is an essential component of an efficient clinical trial program collectively providing the evidence of biosimilarity. In the DRL_RI development program, Study RI-01-003 was a Phase 1/2, randomized, double-blind study comparing the PK and pharmacodynamics (PD) of DRL_RI (biosimilar rituximab) with United States licensed rituximab (Rituxan®, henceforth mentioned as US-rituximab) and European Union (EU)-approved rituximab (MabThera®, henceforth mentioned as EU-rituximab) in subjects with RA. Safety, efficacy, and immunogenicity of the treatments were also compared to those of the innovator reference products in this study. The study met all pre specified primary and secondary endpoints for PK, PD, and efficacy outcomes. The evaluation of safety and immunogenicity upon transition from a registered medicinal product to a biosimilar product is a requirement of US Food and Drug Administration. The objective of the current study is to assess the immunogenicity and safety of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab. Subjects with RA who have received at least 1 full course comprising two 1000 mg infusions with either US-rituximab or EU-rituximab and are candidates for re-treatment with rituximab will be enrolled.

During the initial phase of the clinical use of a newly introduced biosimilar product, it is expected that many subjects will experience a transition from the currently marketed reference product to the biosimilar. Hence, ruling out changes in the safety and immunogenicity of the product upon a single transition from the reference product to the potential biosimilar is a relevant element in the clinical evaluation of the latter.

Objectives:

- To assess the immunogenicity of transitioning subjects with RA to DRL_RI (biosimilar rituximab) from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.
- To assess the safety of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.

Study Population:

Inclusion Criteria

A subject will be eligible for enrolment in the study if he/she meets all of the following criteria:

1. Male or female subjects aged 18 years or older who have provided valid written informed consent.
2. Subjects with a diagnosis of active RA who are eligible for the subsequent treatment course with US-rituximab or EU-rituximab according to the clinical judgment of the investigator.
3. Documented evidence that subject has received at least 1 full course comprising two 1000 mg infusions of either US-rituximab at least 16 weeks prior to the randomization visit or EU-rituximab at least 24 weeks prior to the day of randomization visit.

   Note: Subjects are only eligible if they have received the prior US or EU-rituximab course within the 15 months prior to the date of randomization.
4. Subjects receiving a stable dose of weekly methotrexate (MTX) for at least 4 weeks prior to randomization (between 7.5 mg and 25 mg) and folic acid (at least 5 mg per week).

Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects with RA in functional Class IV (Table 14-2).
2. Subjects with human immunodeficiency virus (positive HIV1Ab or HIV2Ab), hepatitis B virus and/or hepatitis C

virus infection, including those with positive results in the viral disease screening.

3. Subjects with active tuberculosis (TB). Subjects with evidence of latent TB or a history of TB must have completed treatment or have initiated treatment for at least 1 month before the first dose of study treatment (Day 1). TB testing is required only if it is required by local regulations or practice.
4. Active systemic infection.
5. Severely immunocompromised.
6. History of hypersensitivity to either US-rituximab or EU-rituximab or any of its excipients.
7. Any serious illness or uncontrolled medical condition, including, but not limited to, severe infections, significant hepatic or renal disease, uncontrolled hypertension despite treatment (defined as blood pressure ≥160/95 mmHg), congestive heart failure (New York Heart Association [NYHA] Class III or IV), or other severe uncontrolled cardiac disease or uncontrolled diabetes with immediate risk of acute complications.
8. Any condition that in the opinion of the investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for subjects.
9. Requires treatment with any biological medicinal product during the study other than the study treatment.
10. Previous treatment with B-cell modulating or cell-depleting biologic therapy, except US-rituximab or EU-rituximab.
11. Prior participation in this clinical trial or prior participation in any clinical trial with any monoclonal antibody within 12 months of screening or prior participation in any clinical trial within 3 months of screening or within 5 half-lives of the investigational drug or until the expected PD effect has returned to baseline, whichever is longer.
12. Treatment with other biologic disease-modifying anti-rheumatic drugs, or Janus kinase (JAK) inhibitors administered within 12 weeks before the first dose of rituximab of the prior treatment course onwards till the date of randomization.
13. Subjects with the following laboratory abnormalities:
    - Subjects with screening total white blood cell count <3000/µL, platelets <100,000/µL, neutrophils <1500/µL, or hemoglobin <8.5 g/dL.

- Abnormal liver function tests such as aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >2 × upper limit of normal (ULN). A single parameter >2 × ULN can be re-checked as soon as possible, at least prior to randomization, if required per the investigator's discretion.
- Creatinine clearance (Cockcroft & Gault formula) of less than 50 mL/min.

14. History of vaccination with live vaccines within 4 weeks of the first dose of study treatment (Day 1) or known to require live vaccines during the study.
15. Lactating or pregnant female.
16. Women of childbearing potential (WOCBP) who do not consent to use highly effective methods of birth control during treatment and for at least 12 months after the last administration of study treatment.

    Note: Per the Clinical Trial Facilitation Group (CTFG) guidelines 2014, a woman is considered of childbearing potential if fertile, following menarche until becoming postmenopausal (i.e., no menses for 12 months without an alternative medical cause) unless permanently sterile through hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Highly effective birth control measures per CTFG guidelines 2014 include the following:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation - oral, intravaginal, and transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation - oral, injectable, implantable
    - intrauterine device
    - intrauterine hormone-releasing system
    - bilateral tubal occlusion
    - vasectomised partner
    - sexual abstinence

    Site should advise subjects to use any of the methods listed above, or per the country/site-specific requirements.
17. Sexually active male subjects unless permanently sterile by bilateral orchidectomy, who do not agree to use 1 of the highly effective methods of birth control listed in Exclusion Criterion

#16 during treatment and for at least 12 months after the last administration of study treatment.

18. Subject with serum IgG < lower limit of normal

Study Design:

This is a randomized, double-blind, parallel group, multicenter, Phase 3 transition study.

A course of treatment with US-rituximab or EU-rituximab in RA consists of two 1000 mg intravenous (IV) infusions separated by 2 weeks. Subjects with RA who have received at least 1 full course comprising two 1000 mg infusions with either US-rituximab or EU-rituximab will be eligible for the study. For this prior course of treatment, subjects will have received either US-rituximab or EU-rituximab.

Subjects will then be randomized by an interactive web response system (IWRS) to receive either two 1000 mg infusions of DRL_RI (Arm A) or US-rituximab/EU-rituximab (Arm B) on Day 1 and Day 15. This will constitute the next course of rituximab treatment. Subjects randomized to Arm A will receive DRL_RI and subjects randomized to Arm B will continue to receive either US-rituximab or EU-rituximab. The rituximab reference product (US-licensed rituximab [Rituxan] or EU-approved rituximab [Mabthera]) used should be the same in the prior and the randomized treatment course, respectively. Subjects having received the prior treatment course with reference products other than US-licensed rituximab (Rituxan) or EU-approved rituximab (Mabthera) will not be eligible for the study. Subjects should not be switched from the prior to the randomized treatment course from US-licensed to EU-approved reference product or vice versa.

The study will consist of a screening period (Days -14 to 0) and a double-blind period (Day 1 to Week 12). Subjects will attend a screening visit followed by visits at Weeks 0 (Day 1), 2, 4, 8, and 12 (end of study [EOS]) after randomization. An additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP.

Subjects having signed the informed consent form versions prior to the one introduced by this amendment need to re-consent to continue participating in the study after Week 12 through Week 26. If a subject does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.

	If a subject requires rescue therapy after Week 12, then the same can be administered to the subject per investigator's discretion until the additional safety follow-up visit at Week 26. If rituximab re-dosing becomes necessary at a time allowed by the local rituximab label, the same can be administered. Specifics of safety analysis of such subjects will be addressed in the statistical analysis plan. Study procedures include physical examination, vital signs measurement, clinical laboratory assessments, adverse events, and concomitant medications. All subjects completing the study at Week 12 or those discontinuing the study at any time will attend the EOS/early termination visit.
Estimated Study Duration:	Total participation time for a subject in this study is approximately 28 weeks: screening approximately for 2 weeks, treatment for 2 weeks, and follow-up for 24 weeks.
Immunogenicity Assessments:	• Incidence of anti-drug antibodies (ADA), including titer and neutralizing antibodies (NAb).
Safety Assessments:	• Incidence of treatment-emergent adverse events and serious adverse events • Incidence of anaphylactic reactions, hypersensitivity reactions, and infusion-related reactions (IRRs)
Study Treatment, Dosage, and Route of Administration:	The study treatments DRL_RI or US-rituximab/EU-rituximab will be administered as two 1000 mg IV infusions, with the first dose on Day 1 and the second dose on Day 15. Subjects will be pre-medicated before each infusion with acetaminophen, diphenhydramine, and 100 mg IV methylprednisolone or its equivalent to decrease the incidence and severity of acute IRRs. Subjects have to be on a stable dose of weekly MTX (between 7.5 mg and 25 mg) for at least 4 weeks prior to randomization and during the study and folic acid (at least 5 mg per week). Note: MTX and folic acid should be used in accordance with the guidelines specified in the local label (e.g., summary of product characteristics in the EU, US prescribing information for the US). Folinic acid at the same dose of folic acid, can be given in place of folic acid if it is allowed by the local label. Subject should take the same folate supplementation throughout the duration of the study.
Sample Size:	CI [redacted]

CI
CI

CI

Statistical Methods:

Analysis Sets:

- The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment.
- Immunogenicity population will include all subjects with at least 1 post-dose ADA assessment result available.

Analyses of safety parameters will be based on the safety population, and immunogenicity parameters (ADA and NAb) will be based on the immunogenicity population.

Immunogenicity:

Immunogenicity data (ADA and NAb) will be summarized and analyzed descriptively for each scheduled protocol assessment time point by treatment arm and overall.

Safety:

All subjects who are treated with any amount of study treatment will be evaluated for safety. Adverse events will be summarized by the number and percentage of subjects experiencing events by system organ class, preferred term, and severity. Changes in vital signs and clinical laboratory measurements will be summarized descriptively by assessment time points. Other safety variables will be summarized and listed.

Version and Date of Protocol: Version 3.0 Amendment 2; Date: 10 Jul 2020

List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug Antibody
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
Anti-CCP	Anti-citrullinated Peptide
AUC	Area Under The Concentration-time Curve
AUC_{0-t}	AUC from Time Zero to the Last Quantifiable Time Point
β-hCG	Beta Human Chorionic Gonadotropin
BP	Blood Pressure
C1q	C1 q Subcomponent
CD	Cluster of Differentiation
CDC	Complement-dependent Cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence Interval
COVID-19	Coronavirus Disease - 2019
CRO	Clinical Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DAS28	Disease Activity Score
DMARD	Disease-modifying Anti-rheumatic Drug
DRL_RI	Biosimilar Rituximab
DVD	Digital Versatile Disc
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
EOS	End of Study
ET	Early Termination
EU	European Union

Abbreviation	Definition
EULAR	European League Against Rheumatism
Fc	Fragment Crystallizable
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HACA	Human Anti-chimeric antibody
HAQ-DI	Health Assessment Questionnaire Disability Index
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB	Institutional Review Board
IRR	Infusion-related Reaction
IV	Intravenous
IWRS	Interactive Web Response System
JAK	Janus Kinase
LLN	Lower Limit Of Normal
mAb	Monoclonal Antibody
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAb	Neutralizing Antibody
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma

Abbreviation	Definition
PD	Pharmacodynamic(s)
PEI	Paul Ehrlich Institute
PI	Prescribing Information
PK	Pharmacokinetic(s)
QTc	Corrected QT Interval
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Event
TNF	Tumor Necrosis Factor
ULN	Upper Limit Of Normal
US	United States
WOCBP	Women of Childbearing Potential

1 Introduction

Rituximab is licensed in the United States (US) as Rituxan® and approved in the European Union (EU) as MabThera®, for use in B-cell non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia, rheumatoid arthritis (RA) in combination with methotrexate (MTX) in adult patients with moderately to severely active RA who had an inadequate response to 1 or more tumor necrosis factor (TNF) antagonist therapies, granulomatosis with polyangiitis and microscopic polyangiitis in combination with glucocorticoids, and moderate to severe pemphigus vulgaris (Rituxan prescribing information [PI] 2020, MabThera Summary of Product Characteristics [SmPC] 2020). Rituxan is the commercially available product in the US and will be referred to as US-rituximab; MabThera is the commercially available product in the EU and will be referred to as EU-rituximab in the protocol. Rituximab biosimilar (hereafter, referred to as DRL_RI) is being developed as a potential biosimilar to US-rituximab and EU-rituximab.

The term "biosimilar" refers to a biologic drug that is developed to be similar to an existing licensed or approved reference product or reference medicinal product. Biosimilars are intended to treat the same diseases as the reference product/reference medicinal product using the same dose and treatment regimen. Biosimilars are structurally highly similar to their reference products, and minor differences caused by the manufacturing process have no clinically meaningful effect on the pharmacokinetics (PK), safety, immunogenicity, or efficacy of the biosimilar compared with the reference product/reference medicinal product.

In the DRL_RI development program, the primary objective in Study RI-01-003 (Section 1.1.2.2) was to compare the plasma PK profiles of DRL_RI with US-rituximab and EU-rituximab; secondary objectives were to compare the pharmacodynamics (PD), efficacy, safety, and immunogenicity of DRL_RI with US-rituximab and EU-rituximab. The objective of the current study is to assess the immunogenicity and safety of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.

1.1 Background and Rationale

1.1.1 Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal immunoglobulin (Ig) G1 kappa antibody directed against the B-lymphocyte antigen cluster of differentiation

(CD) 20. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM (Rituxan PI 2020, MabThera SmPC 2020).

Rituximab is approved for use in NHL, chronic lymphocytic leukemia, RA, granulomatosis with polyangiitis, microscopic polyangiitis, and moderate to severe pemphigus vulgaris (this indication is currently approved in the United States, but not in the European Union). Further information is contained within both the PI of US-rituximab and public information including the SmPC for EU-rituximab (Rituxan PI 2020, MabThera SmPC 2020).

Multiple clinical trials have been conducted to support the approval of rituximab for the treatment of RA. Rituximab in combination with MTX is indicated for the treatment of adult patients with moderately to severely active RA who had an inadequate response to 1 or more TNF antagonist therapies (Rituxan PI 2020, MabThera SmPC 2020).

1.1.1.1 Mechanism of Action

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95% of all B-cell NHLs. CD20 is found on both normal and malignant B-cells, but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissue(s). This antigen does not internalize upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and thus, does not compete for antibody binding (MabThera SmPC 2020).

The fragment antigen-binding domain of rituximab binds to the CD20 antigen on B lymphocytes and the fragment crystallizable (Fc) domain can recruit immune effector functions to mediate B-cell lysis. Mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from complement component C1 q subcomponent (C1q) binding, and antibody-dependent cellular cytotoxicity mediated by 1 or more of the Fcγ receptors on the surface of granulocytes, macrophages, and natural killer cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis (MabThera SmPC 2020).

Rheumatoid arthritis is an immune-mediated disease of the joints that is characterized by chronic inflammation and synovial hyperplasia that eventually leads to cartilage and bone destruction (Komatsu and Takayanagi 2012). Current treatments include disease-modifying

anti-rheumatic drugs (DMARDs), tofacitinib, glucocorticoids, etc. (Singh et al 2016). B-cells are believed to play a role in the pathogenesis of RA and associated chronic synovitis. In this setting, B-cells may be acting at multiple sites in the autoimmune/inflammatory process, including thorough production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or pro-inflammatory cytokine production (Rituxan PI 2020).

Administration of rituximab in RA patients results in almost complete depletion of peripheral B-cells and variable depletion of B-cells in synovium and other sites such as lymphoid tissue and bone marrow. The degree of B-cell depletion in the peripheral blood and synovium has been correlated positively with the clinical response of rituximab (Mok CC 2014, Cohen MD and Keystone E 2015).

1.1.1.2 Pharmacodynamics

In RA patients, immediate depletion of B-cells in the peripheral blood was observed following 2 infusions of 1000 mg rituximab separated by a 14-day interval. The majority of patients demonstrated near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/µL) within 2 weeks after receiving the first dose of rituximab. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment. Peripheral blood B-cell counts began to increase from Week 24 (during the follow-up period) and evidence for repopulation was observed in the majority of patients by Week 40 (Dr. Reddy's Laboratories Investigator's Brochure [IB]).

Total serum Ig levels, immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA) were decreased at 6 months with the largest change observed in IgM. At Week 24 of the first course of rituximab treatment, small proportions of patients experienced decrease in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with rituximab in RA patients during repeated rituximab treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA, respectively concentrations below the LLN at any time after receiving rituximab. The clinical consequences of decrease in Ig levels in RA patients treated with rituximab are unclear (Dr. Reddy's Laboratories IB).

Treatment with rituximab in patients with RA was associated with reduction of certain biological markers of inflammation such as interleukin-6, C-reactive protein (CRP), serum amyloid protein, S100 A8/S100 A9 heterodimer complex, anti-citrullinated peptide (anti-CCP), and RF (Dr. Reddy's Laboratories IB).

1.1.1.3 Efficacy in Rheumatoid Arthritis

The efficacy and safety of rituximab in alleviating the symptoms and signs of RA in subjects with an inadequate response to TNF inhibitors was demonstrated in a pivotal randomized, controlled, double-blind, multicenter study. The study evaluated 517 RA subjects who had experienced an inadequate response or intolerance to 1 or more TNF inhibitor therapies. Rituximab was administered as 2 intravenous (IV) infusions separated by an interval of 15 days. Subjects received two 1000 mg IV infusions of rituximab or placebo in combination with MTX. All subjects received concomitant 60 mg oral prednisone on Days 2 to 7 and 30 mg on Days 8 to 14 following the first infusion. The primary endpoint was the proportion of subjects who achieved at least 20% improvement in American College of Rheumatology (ACR) score (ACR20) at Week 24. Subjects were followed beyond Week 24 for long-term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of subjects from the original placebo group received rituximab between Week 24 and Week 56, under an open-label extension study protocol (MabThera SmPC 2020).

Disease Activity Outcomes

Rituximab in combination with MTX significantly increased the proportion of subjects achieving ACR20 compared with subjects treated with MTX alone. Clinically and statistically, significant improvement was also noted in all individual components of the ACR response (tender and swollen joint counts, subject and physician global assessment, Health Assessment Questionnaire Disability Index [HAQ-DI], pain assessment, and CRP). Subjects treated with rituximab in combination with MTX had a significantly greater reduction in Disease Activity Score 28 (DAS28) than subjects treated with MTX alone. Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more subjects treated with rituximab and MTX compared to subjects treated with MTX alone (MabThera SmPC 2020).

Radiographic Response

Structural joint damage was assessed radiographically and expressed as change in modified total sharp score and its components, the erosion score, and joint space narrowing score. Subjects with inadequate response or intolerance to 1 or more TNF inhibitor therapies, receiving rituximab in combination with MTX demonstrated significantly less radiographic progression than subjects originally receiving MTX alone at 56 weeks. Of the subjects originally receiving MTX alone, 81% received rituximab either as a rescue between Week 16 to Week 24 or in the extension trial before Week 56. A higher proportion of subjects receiving the original rituximab/MTX treatment also had no erosive progression over 56 weeks (MabThera SmPC 2020).

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years demonstrated significantly reduced progression of structural joint damage in subjects receiving rituximab in combination with MTX compared to MTX alone as well as a significantly higher proportion of subjects with no progression of joint damage over the 2-year period (MabThera SmPC 2020).

Physical Function and Quality of Life Outcomes

Significant reductions in HAQ-DI and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]) scores were observed in subjects treated with rituximab compared to subjects treated with MTX alone. The proportions of rituximab-treated subjects showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among subjects receiving MTX alone (MabThera SmPC 2020).

Significant improvement in health-related quality of life was also demonstrated with significant improvement in both the physical health score and mental health score of the Short Form 36 (SF-36) Health Survey. Further, a significantly higher proportion of subjects achieved MCIDs for these scores (MabThera SmPC 2020).

Efficacy in Autoantibody (RF and/or anti-CCP) Seropositive Subjects

Subjects seropositive to RF and/or anti-CCP who were treated with rituximab in combination with MTX showed an enhanced response compared with subjects negative to both. Efficacy

outcomes in rituximab-treated subjects were analyzed based on autoantibody status prior to commencing treatment. At Week 24, subjects who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and ACR50 responses compared to seronegative subjects (P=0.0312 and P=0.0096). These findings were replicated at Week 48, where autoantibody seropositivity also significantly increased the probability of achieving ACR70. At Week 48, seropositive subjects were 2 to 3 times more likely to achieve ACR responses compared to seronegative subjects. Seropositive subjects also had a significantly greater decrease in DAS28-erythrocyte sedimentation rate compared to seronegative subjects (MabThera SmPC 2020).

Long-Term Efficacy With Multiple Course Therapy

Treatment with rituximab in combination with MTX over multiple courses resulted in sustained improvements in the clinical signs and symptoms of RA, as indicated by ACR, DAS28-erythrocyte sedimentation rate, and EULAR responses, which were evident in all subject populations studied. Sustained improvements in physical function as indicated by the HAQ-DI score and the proportion of subjects achieving MCID for HAQ-DI were observed (MabThera SmPC 2020).

Other clinical studies conducted to demonstrate the efficacy of rituximab in RA subjects had similar results (Mok CC 2014, Cohen MD and Keystone E 2015, and Rituxan PI 2020).

1.1.1.4 Safety Profile

The overall safety profile of rituximab in RA is based on data from patients from clinical trials and from post-marketing surveillance (MabThera SmPC 2020).

In clinical trials more than 3100 subjects received at least 1 treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 subjects received 2 or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post-marketing experience reflects the expected adverse reaction profile as seen in clinical trials for rituximab (MabThera SmPC 2020).

The most frequent adverse drug reactions (ADRs) following receipt of rituximab in clinical studies were infusion-related reactions (IRRs). Among the 3189 subjects treated with rituximab, 1135 (36%) experienced at least 1 IRR with 733/3189 subjects (23%) experiencing an IRR following first infusion of the first exposure to rituximab. The incidence of IRRs

declined with subsequent infusions. In clinical trials, fewer than 1% (17/3189) of subjects experienced a serious IRR. There were no common terminology criteria for adverse events (CTCAE) Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTCAE Grade 3 events and of IRRs leading to withdrawal decreased by course, and such events were rare from Course 3 onwards. Pre-medication with IV glucocorticoid significantly reduced the incidence and severity of IRRs. Severe IRRs with fatal outcome have been reported in the post marketing setting (MabThera SmPC 2020).

Other ADRs reported in greater than 10% of subjects in clinical studies or during post-marking surveillance in patients with RA receiving rituximab included upper respiratory tract infection, urinary tract infection, headache, and decreased IgM levels (MabThera SmPC 2020).

The overall rate of infection was approximately 94 per 100 patient-years in rituximab-treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient-years. Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of rituximab for the treatment of autoimmune diseases, including RA. Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving rituximab (MabThera SmPC 2020).

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first rituximab exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation, and infections, all of which were more frequent in the first 6 months of treatment (MabThera SmPC 2020).

1.1.1.5 Immunogenicity

As rituximab is a chimeric monoclonal antibody (mAb), the development of human anti-chimeric antibodies (HACAs) lower the level of the drug and hence, its clinical efficacy is a concern (Mok CC 2014).

A pooled analysis on the long-term safety of rituximab in clinical trials (2578 subjects) revealed that HACAs were present in 11% of subjects on at least 1 visit. There was no obvious relationship between the dose of rituximab used (500 mg versus 1000 mg) and the incidence

of the HACA response. The presence of HACAs to rituximab does not appear to affect the efficacy of rituximab in depleting B-cells, clinical efficacy at the study endpoints, and re-treatment efficacy. There is also no obvious relationship between the HACA response and the occurrence of infusion reactions to rituximab (Mok CC 2014).

1.1.2 Dr. Reddy's Rituximab (DRL_RI)

Dr. Reddy's Laboratories S.A. (DRL) is developing a proposed biosimilar version of the chimeric anti-CD20 mAb, rituximab (DRL_RI).

DRL_RI is a chimeric human/murine IgG1 kappa mAb consisting of murine light and heavy chain variable regions and human constant region sequences. The molecule is composed of 2 heavy chains of 451 amino acids each and 2 light chains of 213 amino acids each with a molecular weight of 145 kilodaltons. Each of the heavy chains contains 1 N-linked glycan (resulting in 2 N-linked glycans per molecule).

The primary amino acid sequence is identical and the secondary and tertiary structures of DRL_RI are indistinguishable from the reference products (US-rituximab and EU-rituximab) when compared by a battery of orthogonal analytical methods. The glycosylation variants (glycoforms) of DRL_RI are the same as those found in the reference products, and the proportions of each of the glycoforms are similar between the 3 proteins.

Further information can be found in the IB for DRL_RI (Dr. Reddy's Laboratories IB).

1.1.2.1 Nonclinical Studies

In Vitro Pharmacology

The comparison of in vitro functional activities of DRL_RI, US-rituximab, and EU-rituximab were performed using multiple cell-based and binding assays. Batches of DRL_RI, US-rituximab, and EU-rituximab were compared using 2 one-sided t-test analyses. A difference of 20% in the mean relative binding or potency was deemed acceptable. The complement dependent cytotoxicity (CDC) and the antibody-dependent cell-mediated cytotoxicity (ADCC) activities and the binding of DRL_RI, US-rituximab, and EU-rituximab to CD20, C1q, FcγRI, FcγRIIa, FcγRIIb, FcγRIII, and FcRn were found to be similar. Therefore, DRL_RI, US-rituximab, and EU-rituximab are considered similar in terms of their in vitro functional characteristics (Dr. Reddy's Laboratories IB).

1.1.2.2 Clinical Studies

Study RI-01-003 was a Phase 1/2, randomized, double-blind study, conducted in subjects with RA to compare PK, PD, efficacy, safety, and immunogenicity of DRL_RI with US-rituximab and EU-rituximab.

The PK endpoint results showed that the 91% confidence interval (CI) for the geometric mean of the test to reference ratios of all endpoints were within the pre specified similarity acceptance range of 80.00% to 125.00% for the comparisons of DRL_RI with EU-rituximab and US-rituximab, and for the comparison of EU-rituximab with US-rituximab, demonstrating the PK similarity of the 3 products. The primary PK endpoints were area under the concentration-time curve (AUC) from time zero extrapolated to infinity for both study treatment infusions, AUC from start to the first infusion to the second infusion on Day 14 after the first infusion, and AUC from time zero to the last quantifiable time point (AUC_{0-t}) after the second infusion of study treatment. The secondary PK endpoints were AUC_{0-t} over the entire treatment course and maximum plasma concentration (C_{max} after the first and after the second infusion. Results from the secondary endpoints of Study RI-01-003 also showed that the safety and immunogenicity profiles; CD20-positive peripheral blood B-cell count reductions; the proportion of subjects meeting the ACR20, ACR50, and ACR70 improvement criteria from baseline to Week 24; and the mean change from baseline to Week 24 in DAS28-CRP, were all comparable across DRL_RI, US-rituximab, and EU-rituximab.

1.1.3 Study Rationale

The evaluation of PK, efficacy, safety, and immunogenicity between a biosimilar and the innovator product is an essential component of an efficient clinical trial program collectively providing the evidence of biosimilarity. In the DRL_RI development program, Study RI-01-003 was a Phase 1/2, randomized, double-blind study comparing the PK and PD of DRL_RI with US-rituximab and EU-rituximab in subjects with RA. Safety, efficacy, and immunogenicity of the treatments were also compared to those of the innovator reference products in this study. The study met all pre specified primary and secondary endpoints for PK, PD, and efficacy outcomes (Section 1.1.2.2).

The evaluation of safety and immunogenicity upon transition from a registered medicinal product to a biosimilar product is a requirement of US Food and Drug Administration (FDA). The objective of the current study is to assess the immunogenicity and safety of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab. Subjects with RA, who have received at least 1 full course comprising two 1000 mg infusions with either US-rituximab or EU-rituximab and are candidates for re-treatment with rituximab, will be enrolled.

During the initial phase of the clinical use of a newly introduced biosimilar product, it is expected that many patients will experience a transition from the currently marketed reference product to the biosimilar. Hence, ruling out changes in the safety and immunogenicity of the product upon a single transition from the reference product to the potential biosimilar is a relevant element in the clinical evaluation of the latter.

1.1.4 Risk/Benefit and Ethical Assessment

There is a substantial body of data related to the safety and efficacy of US-rituximab/EU-rituximab in subjects with RA (FDA, Rituxan PI/European Medicines Agency MabThera SmPC) (Rituxan PI 2020, MabThera SmPC 2020). Preliminary results of a comprehensive head-to-head comparison of DRL_RI to the US-rituximab and the EU-rituximab has demonstrated that DRL_RI is similar to the reference products (Section 1.1.2). Thus, the risk/benefit of DRL_RI is expected to be comparable to that of US-rituximab/EU-rituximab.

More detailed information about the known and expected benefits/risks and expected adverse events (AEs) of DRL_RI may be found in the IB for DRL_RI (Dr. Reddy's Laboratories IB).

2 Study Objectives and Endpoints

Table 2-1 Objectives and Endpoints

Objectives	Endpoints
To assess the immunogenicity of transitioning subjects with RA to DRL_RI (biosimilar rituximab) from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.	The immunogenicity endpoint is: The incidence of anti-drug antibodies (ADA), including titer and neutralizing antibodies (NAb).
To assess the safety of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab.	The primary safety endpoints are: • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). • Incidence of anaphylactic reactions, hypersensitivity reactions, and IRRs. Other safety endpoints are: • Clinical laboratory parameters • Vital signs • Twelve-lead electrocardiograms (ECG) • Physical examination

Abbreviations: EU, European Union; IRR, infusion-related reactions; RA, rheumatoid arthritis; US, United States.

3 Investigational Plan

3.1 Study Design

3.1.1 Description

This is a randomized, double-blind, parallel group, multicenter, Phase 3 transition study in subjects with active RA who are eligible for the subsequent treatment course with US-rituximab or EU-rituximab according to the clinical judgment of the investigator.

It is planned to randomize 140 subjects (70 per treatment arm) at approximately 50 sites in up to 7 countries (including, but not restricted to the United States).

A course of treatment with US-rituximab or EU-rituximab in RA consists of two 1000 mg IV infusions separated by 2 weeks. Subjects with RA who have received at least 1 full course comprising two 1000 mg infusions with either US-rituximab or EU-rituximab will be eligible for the study. The rituximab reference product (US-licensed rituximab [Rituxan] or EU-approved rituximab [Mabthera]) used should be the same in the prior and the randomized treatment course, respectively. Subjects having received the prior treatment course with reference products other than US-licensed rituximab (Rituxan) or EU-approved rituximab (Mabthera) will not be eligible for the study. Subjects should not be switched from the prior to the randomized treatment course from US-licensed to EU-approved reference product or vice versa.

Subjects will then be randomized by interactive web response system (IWRS) to receive either two 1000 mg infusions of DRL_RI (Arm A) or US-rituximab/EU-rituximab (Arm B) on Day 1 and Day 15. This will constitute the next course of rituximab treatment. Subjects randomized to Arm A will receive DRL_RI and subjects randomized to Arm B will continue to receive either US-rituximab or EU-rituximab.

The study will consist of a screening period (Days -14 to 0) and a double-blind period (Day 1 to Week 12). Subjects will attend a screening visit followed by visits at Weeks 0 (Day 1), 2, 4, 8, and 12 (end of study [EOS]) after randomization. An additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in women of childbearing potential (WOCBP).

Subjects having signed the informed consent form (ICF) versions prior to the one introduced by this amendment need to re-consent to continue participating in the study after Week 12 through Week 26. If a subject does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.

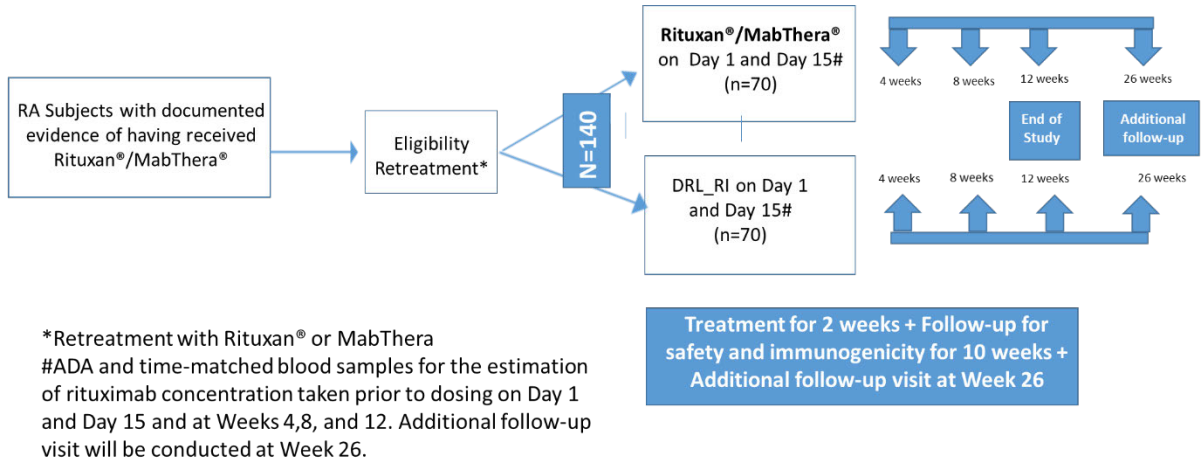
If a subject requires rescue therapy after Week 12, then the same can be administered to the subject per investigator's discretion until the additional safety follow-up visit at Week 26. If rituximab re-dosing becomes necessary at a time allowed by the local rituximab label, the same can be administered. Specifics of safety analysis of such subjects will be addressed in the statistical analysis plan (SAP). Study procedures include physical examination, vital signs measurement, clinical laboratory assessments, AEs, and concomitant medication. All subjects completing the study at Week 12 or those discontinuing the study at any time will attend an EOS/early termination (ET) visit.

The study endpoints are the incidence of anti-drug antibodies (ADA), including titer and neutralizing antibodies (NAbs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), anaphylactic reactions, hypersensitivity reactions, and IRRs. The subject's response to treatment will be assessed in accordance with usual clinical practice.

Samples for the evaluation of ADA will be obtained before the administration of study treatment on Day 1 and Day 15. Additional samples for detection of ADA will be collected at Weeks 4, 8, and 12 (EOS/ET visit). Samples that are confirmed positive for ADA will be further tested for titer and NAb. Details are described in Section 6.2.

A study scheme is provided in Figure 3-1.

Figure 3-1 Study Scheme



Abbreviations: ADA, anti-drug antibody; DRL_RI, biosimilar rituximab; N, total number of subjects; n, number of subjects in each treatment arm; RA, rheumatoid arthritis.

Data until Week 12 will be analyzed and reported in the final Clinical Study Report (CSR) after all subjects complete Week 12 visit (EOS/ET). The subsequent follow-up data from Week 12 to Week 26 will be reported as an addendum to the final CSR and for the data up to and including the Week 12 or ET visit.

3.1.2 Rationale of Study Design

This is a randomized, double-blind, parallel group, multicenter study designed to assess the immunogenicity of transitioning subjects with RA to DRL_RI from US-rituximab/EU-rituximab to continued treatment with US-rituximab/EU-rituximab. The study is part of the DRL_RI development program to support DRL_RI as a biosimilar. The comparators used in this study are US-licensed rituximab (Rituxan) or EU-approved rituximab (MabThera).

The parallel and double-blinded design study also allows for independent assessment of safety and immunogenicity of the DRL_RI arm of the study relative to the control arms in these population to support registration. It also allows for the 2 control arms to be evaluated relative to each other. Randomization prevents the selection bias and insures against the accidental bias.

Subjects who have received at least 1 full course comprising two 1000 mg infusions of either US-rituximab or EU-rituximab and are candidates for re-treatment with rituximab will be

enrolled. DRL_RI will be administrated in combination with MTX as two 1000 mg infusions on Day 1 and Day 15, which is consistent with the recommended dose for RA as described in the PI of Rituxan and the SmPC for MabThera (Rituxan PI 2020, MabThera SmPC 2020).

Study endpoints are the incidence of ADA, including titer and NAb; TEAEs; and SAEs, anaphylactic reactions, hypersensitivity reactions, and IRRs. Samples for the evaluation of ADA will be obtained before the administration of study treatment on Day 1 and Day 15, and at Weeks 4, 8, and 12 (EOS/ET) visits. Samples that are confirmed positive for ADA will be further tested for titer and NAb. An additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP.

A validated enzyme-linked immunosorbent assay (ELISA) will be used to test ADA, titer and NAb by specialist laboratories (sponsor designated laboratories) in this study.

Along with immunogenicity sample, a time-matched blood sample (approximately 5 mL) will be collected for the estimation of rituximab concentration. The evaluation of the samples will be performed to interpret safety and/or immunogenicity data appropriately, if needed.

3.1.3 Early Termination of the Study

This study may be terminated prematurely at any time by Dr. Reddy's Laboratories S.A. for medical, operational, or ethical reasons at individual or all study sites.

If the study is prematurely terminated or discontinued, Dr. Reddy's Laboratories S.A./clinical research organization (CRO) will promptly notify the investigators, institutions, and all competent regulatory authorities in writing outlining the reasons for the termination. The investigator or Dr. Reddy's Laboratories S.A./CRO will promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). After notification, the investigator must contact all participating subjects and the hospital pharmacies (if applicable) within a reasonable time period and inform them of the premature termination/discontinuation of the study.

The clinical research associate will contact the investigators to schedule a close-out visit for all participating sites.

As directed by Dr. Reddy's Laboratories S.A./CRO, all unused study documents/materials (for e.g., study drugs, packing slips, stickers, etc.) shall be collected. All electronic case report

forms (eCRFs) will be completed. All documents required for archiving at the site will be retained at the site itself. The study monitor will ensure that any outstanding data clarification issues and queries are resolved, and that all study records at the study site are complete.

3.1.4 End of Study

End of study is defined as the time at which all subjects enrolled in the study have been followed for 10 weeks after treatment unless lost to follow-up or the subject has died. The EOS is achieved at the last subject's Week 12 visit. After EOS, an additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP.

3.2 Study Conduct During the COVID-19 Pandemic

Coronavirus disease of 2019 (COVID-19) is a viral illness caused by the novel coronavirus (also called the SARS-CoV-2) and has impacted most of the countries across the globe. It was declared as a global public health emergency by the World Health Organization on 30 Jan 2020. This pandemic has impacted the conduct of clinical trials in various ways.

3.2.1 Benefit-Risk Assessment of Rituximab Treatment During the COVID-19 Pandemic

Rituximab is a known immunosuppressant drug and immunosuppression/immunomodulation is the known mechanism of action for its various approved indications and clinical use, including its use in RA.

The current knowledge about human immune response to COVID-19 is limited. It is also not precisely known whether patients on rituximab are associated with a higher risk or with a higher severity of COVID-19. However, given the general immunosuppressive nature, it cannot be ruled out entirely. Methotrexate used concomitantly with rituximab in the treatment of RA is also a known immunosuppressant. It is known to increase the risk of opportunistic infections and has to be avoided during active infection.

Rheumatoid arthritis is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually affecting the skin, eyes, heart, kidneys, and lungs. At the advanced stage it leads to deformities and bone erosion, usually very painful for a patient (Komatsu and Takayanagi 2012; Bullock et al 2018). Moreover, there could be worsening of the disease, if the patient is deprived of the treatment. Hence, it is important to analyse the benefit-risk ratio for a particular patient on a case to case basis.

Moreover, per recommendation by the ACR, in patients with moderate to high disease activity despite optimal conventional synthetic DMARDs, biologics may be started (Mikuls TR et al 2020). In patients already on biologics who need a switch to rituximab, the same considerations would be expected to apply.

Hence, based on the above considerations, the benefit of rituximab treatment outweigh the risks associated with the current COVID-19 situation provided all steps are taken towards ensuring the subject interest and various contingency and safety measures are implemented towards the same. Various such measures have been taken to ensure safety and to minimize the risks for the subjects in compliance with the various recommendations and regulatory guidelines as well as disease management guidelines.

3.2.2 Contingency Measures Taken During the COVID-19 Pandemic

Based upon the above mentioned considerations, the following measures have been implemented in the study:

1. COVID-19 protective measures: Advice to the sites to implement general hygienic measures for both ongoing subjects and any new subject to educate on such protective and preventive measures.

2. Assurance of subject safety by investigator before enrolment (by COVID-19 related screening questionnaire).

3. Measures to be taken if investigator suspect COVID-19-related symptoms or if a subject is found positive to COVID-19.

4. In order to protect subject's safety and welfare, it is also recommended that site contacts subjects periodically (preferably on Day 7, 14; Weeks 6, 10, 14, 18, and 22) via telephone to inquire about his/her overall well-being, to seek information on alarm symptoms (fever, cough, breathlessness, COVID-19-related skin lesion, etc) of COVID-19 infection, information on subject's contact with any COVID-19-positive patient, and to guide the subject to take appropriate medical care.

   If a study subject has an event suspected to be COVID-19 related, the investigator will have to decide on performing COVID-19 testing per local health authority or study site guidance.

Any new AE or change in the intensity of ongoing AE(s) with special focus on symptoms related to COVID-19, new medication(s) taken by the subject since his/her last visit, or any change in dose/frequency of medication(s), which is received, will be also documented in the source documents and eCRF.

5. Any event of COVID-19 is to be considered as an "Event of Special Interest" and all relevant detailed information will be collected, such as diagnosis, management and outcome. All events related to or linked to COVID-19 and meeting SAE criteria must be reported to CI Pharmacovigilance within 24 hours of the investigator's knowledge of the event by facsimile or other appropriate method.

   Moreover, due to current COVID-19 pandemic situation, remote source data verification may be performed per local regulations. All details of remote monitoring will be captured in the monitoring plan, if required.

   A detailed information about the type of data to be collected, handing of missing data or assessment/procedure will be captured in the eCRF filling guidelines/data management plan if required. Listings/summaries of all subjects affected due to COVID-19, including protocol deviations, additional safety contingency measures will be generated based on the available data if required. Corresponding details will be mentioned in the SAP.

   If COVID-19 wanes off, the sponsor may not collect COVID-19-specific data (as mentioned above) and may not follow-up with the subject for COVID-19-related information. In such a case, the CRO and site will be notified for further action.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 140 subjects will be enrolled at approximately 50 sites in up to 7 countries. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

A subject will be eligible for enrolment in the study if he/she meets all of the following criteria:

1. Male or female subjects aged 18 years or older who have provided valid written informed consent.
2. Subjects with a diagnosis of active RA who are eligible for the subsequent treatment course with US-rituximab or EU-rituximab according to the clinical judgment of the investigator.
3. Documented evidence that subject has received at least 1 full course comprising two 1000 mg infusions of either US-rituximab at least 16 weeks prior to the randomization visit or EU-rituximab at least 24 weeks prior to the day of randomization visit.

   Note: Subjects are only eligible if they have received the prior US or EU-rituximab course within the 15 months prior to the date of randomization.
4. Subjects receiving a stable dose of weekly MTX for at least 4 weeks prior to randomization (between 7.5 mg and 25 mg) and folic acid (at least 5 mg per week).

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects with RA in functional Class IV (Table 14-2).

2. Subjects with human immunodeficiency virus (positive HIV1Ab or HIV2Ab), hepatitis B virus and/or hepatitis C virus infection, including those with positive results in the viral disease screening (Section 6.1.1).
3. Subjects with active tuberculosis (TB). Subjects with evidence of latent TB or a history of TB must have completed treatment or have initiated treatment for at least 1 month before the first dose of study treatment (Day 1). TB testing is required only if it is required by local regulations or practice.
4. Active systemic infection.
5. Severely immunocompromised.
6. History of hypersensitivity to either US-rituximab or EU-rituximab or any of its excipients.
7. Any serious illness or uncontrolled medical condition, including, but not limited to, severe infections, significant hepatic or renal disease, uncontrolled hypertension despite treatment (defined as blood pressure [BP] ≥160/95 mmHg), congestive heart failure (New York Heart Association [NYHA] Class III or IV), or other severe uncontrolled cardiac disease or uncontrolled diabetes with immediate risk of acute complications.
8. Any condition that in the opinion of the investigator represents an obstacle for study conduct and/or represents a potential unacceptable risk for subjects.
9. Requires treatment with any biological medicinal product during the study other than the study treatment.
10. Previous treatment with B-cell modulating or cell-depleting biologic therapy, except US-rituximab or EU-rituximab.
11. Prior participation in this clinical trial or prior participation in any clinical trial with any monoclonal antibody within 12 months of screening or prior participation in any clinical trial within 3 months of screening or within 5 half-lives of the investigational drug or until the expected PD effect has returned to baseline, whichever is longer.
12. Treatment with other biologic DMARDs, or Janus kinase (JAK) inhibitors administered within 12 weeks before the first dose of rituximab of the prior treatment course onwards till the date of randomization.

13. Subjects with the following laboratory abnormalities:

    - Subjects with screening total white blood cell count <3000/µL, platelets <100,000/µL, neutrophils <1500/µL, or hemoglobin <8.5 g/dL.
    - Abnormal liver function tests such as aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >2 × upper limit of normal (ULN). A single parameter >2 × ULN can be re-checked as soon as possible, at least prior to randomization, if required as per the investigator's discretion.
    - Creatinine clearance (Cockcroft & Gault formula) of less than 50 mL/min.

14. History of vaccination with live vaccines within 4 weeks of the first dose of study treatment (Day 1) or known to require live vaccines during the study.
15. Lactating or pregnant female.
16. Women of childbearing potential who do not consent to use highly effective methods of birth control during treatment and for at least 12 months after the last administration of study treatment.

    Note: Per the Clinical Trial Facilitation Group (CTFG) guidelines 2014, a woman is considered of childbearing potential if fertile, following menarche until becoming postmenopausal (i.e., no menses for 12 months without an alternative medical cause) unless permanently sterile through hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Highly effective birth control measures per CTFG guidelines 2014 include the following:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation - oral, intravaginal, and transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation - oral, injectable, and implantable
    - intrauterine device
    - intrauterine hormone-releasing system
    - bilateral tubal occlusion
    - vasectomised partner
    - sexual abstinence

Site should advise subjects to use any of the methods listed above, or per the country/site-specific requirements.

17. Sexually active male subjects unless permanently sterile by bilateral orchidectomy, who do not agree to use 1 of the highly effective methods of birth control listed in Exclusion Criterion #16 during treatment and for at least 12 months after the last administration of study treatment.
18. Subjects with serum IgG <LLN.

4.2 Withdrawal of Subjects From Study Treatment and/or the Study

The duration of the study is defined for each subject as the date when signed written ICF is provided through the EOS visit on Week 12. An additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP. Subjects having signed the ICF versions prior to the one introduced by this amendment need to re-consent to continue participating in the study after Week 12 through Week 26. If a subject does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. The subject does not meet the protocol inclusion or exclusion criteria before the last scheduled dose of study treatment is administered. If the first dose of study drug was already administered, the subject should not receive the second dose of study drug, but study follow-up should be completed.
2. The subject is noncompliant with the protocol that in the investigator's opinion requires withdrawal from the study.
3. The subject has a serious or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study.
4. The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.

5. The subject is lost to follow-up.
6. Other reasons (e.g., pregnancy, development of contraindications of use of study treatment).
7. The subject withdraws consent from study participation or from further treatment, or the investigator or sponsor decides to discontinue the subject's participation for a specific safety reason in the study, or the subject does not re-consent to continue participation in the study after Week 12.

Note: If a subject withdraws consent for further study treatment, but not for study participation, the subject can continue further visits and data can continue to be collected until Week 26. However, if a subject withdraws consent for further participation in the study there will be no further data collection and the subject will be discontinued from the study. If a subject having signed the ICF versions prior to the one introduced by this amendment does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study. If Dr. Reddy's Laboratories S.A. terminates the study all subjects will be withdrawn.

Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor before withdrawing the subject. If a subject is discontinued because of an AE, the event will be followed until it is resolved, or it is deemed in the opinion of the investigator that the AE is stabilized and further follow-up is not required. Any subject may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

During the study, the subjects can independently withdraw from study treatment and/or study participation at any time. Also, the subjects may be withdrawn from the study at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way. If a subject does not return for a scheduled visit, every effort will be made to contact the subject. All attempts to contact the subject and information received during contact attempts (3 attempts with minimum 2 different modes to follow-up/contact) must be documented in the subject's medical record. In any circumstance,

every effort will be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and request the subject to return for the EOS/ET (Week 12) visit, if applicable, and follow-up with the subject regarding any unresolved AEs. An additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP. The investigator or sub-investigator or designee will be responsible for reporting subject withdrawal to Dr. Reddy's Laboratories S.A./CRO. Subjects withdrawn from the study cannot be re-enrolled at a later time, regardless of the reason for withdrawal. The reason of withdrawal should be provided in the eCRF.

If the subject withdraws consent for further treatment, but consents to study participation, data will continue to be collected until Week 26.

Subjects having signed the ICF versions prior to the one introduced by this amendment need to re-consent to continue participating in the study after Week 12 through Week 26. If a subject does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.

If a subject withdraws consent from study participation after Week 12 but before the additional follow-up visit at Week 26, he/she will be required to undergo the Week 26 assessments on the day of study discontinuation. If a subject consents to undertake additional and optional study procedures/assessments but withdraws consent for doing so at a later visit, he/she will be retained in the study for the routine study procedures/assessments.

If a subject withdraws from the study and also withdraws consent for disclosure of future information, the subject will undergo ET visit assessments. Dr. Reddy's Laboratories S.A./CRO may retain and continue to use any data collected before such withdrawal of consent.

4.2.3 Replacements

Subjects who withdraw or discontinue after randomization are not to be replaced.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Arms

After written informed consent is obtained from an eligible subject, a unique subject identification number will be assigned to this subject at screening visit. Subjects will be identified during the whole study only by their assigned subject identification number.

Subjects will be randomly assigned at the baseline/randomization visit (Day 1) to receive DRL_RI or US-rituximab or EU-rituximab using a 1:1 allocation ratio. An IWRS will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using statistical analysis system (SAS) software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina, US) for IWRS, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be stratified by region (US/EU). It will also use an appropriate block size, which will not be revealed.

Dispensing of study treatment will be coordinated by IWRS on Day 1 and Day 15. The system will assign a kit number corresponding to the randomization arm by region (US/EU).

Randomization plan document will be prepared before the generation of randomization schedule. The randomization code will be computer-generated and kept by a statistician independent from the project team.

This randomization number identifies which treatment will be allocated to each subject. The subject identification number of subjects who withdraw or discontinue before or after the randomization will not be re-used.

5.2 Treatments Administered

This is a randomized, double-blind, and parallel group clinical study.

Following signing of ICF, subjects will be registered into the study to receive a unique subject identification number. Randomization will be performed using an IWRS. Subjects will be randomized in a 1:1 ratio to 1 of the 2 study treatment arms as follows:

- Arm A: DRL_RI (proposed rituximab biosimilar)
- Arm B: US-rituximab or EU-rituximab

The study treatments DRL_RI or US-rituximab/EU-rituximab will be administered as two 1000 mg IV infusions separated by 2 weeks (Section 5.2.3). Subjects will be pre-medicated before each infusion (Section 5.2.2).

5.2.1 Study Treatment Infusion Preparation

Study treatment (DRL_RI or US-rituximab/EU-rituximab) solutions for infusion will be prepared by unblinded pharmacist designated as site team member in this study. Study treatment will be administered by IV infusion. It **should not** be administered as an IV push or bolus.

Pharmacists should use aseptic techniques appropriate to parenteral administration projects. Study treatment vials and prepared solutions should be inspected visually for particulate matter and discoloration prior to administration. The necessary amount of study treatment will be withdrawn and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% sodium chloride, United States Pharmacopeia, or 5% dextrose Injection, United States Pharmacopeia. The infusion bag should be gently inverted to mix the solution. Do not use vials if particulates or discoloration are present. Further information can be obtained in the pharmacy manual.

5.2.2 Pre-medication for Study Treatment Infusions

Pre-medication consisting of an antipyretic and an antihistamine (e.g., paracetamol [acetaminophen] and diphenhydramine) should always be administered before each infusion of rituximab.

All subjects should also receive pre-medication with 100 mg IV methylprednisolone or its equivalent to be completed at least 30 minutes prior to rituximab infusions to decrease the incidence and severity of acute IRRs.

Acute IRRs are most often observed during the first infusion of rituximab. Any reduction in use of pre-medications during subsequent infusion must be in compliance with local labelling and regulation(s).

5.2.3 Study Treatment Administration

Study treatments (DRL_RI or US-rituximab/EU-rituximab) will be administered by IV infusion using the escalating infusion rate described in the Health Authority-approved product

labels for US-rituximab/EU-rituximab. The infusion rate must be well controlled to reduce the incidence of serious IRRs.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biological agents.

Study treatment infusions should be administered under close medical supervision and in an environment where full resuscitation facilities are immediately available. Vital signs will be monitored every 30 minutes (± 5 minutes) during the course of the treatment administration or more frequently as necessary.

The study treatments will be administered as two 1000 mg IV infusions on Day 1 and Day 15.

Below instructions should be followed in consolidation with the local product labelling if it differs from these instructions.

- **First infusion (Day 1)**: Initiate infusion at a rate of 50 mg/hour. In the absence of infusion toxicity, increase infusion rate by 50 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.
- **Second infusion (Day 15)**: Initiate infusion at a rate of 100 mg/hour. In the absence of infusion toxicity, increase rate by 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.
- Subjects should be closely monitored post-dose for at least 1 hour for the onset of IRRs. Subjects who develop evidence of severe reactions, especially severe dyspnea, bronchospasm, or hypoxia should have the infusion interrupted immediately. In all subjects, the infusion should not be restarted until complete resolution of all symptoms and normalization of laboratory values is achieved. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis.
- Mild to moderate IRRs usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

5.3 Identity of Investigational Product

Proposed rituximab biosimilar (DRL_RI) or US-rituximab/EU-rituximab will be provided as study treatment to the participating sites.

DRL_RI and US-rituximab/EU-rituximab will be supplied as sterile, preservative-free, non-pyrogenic, single-use vials. Each 100 mg vial will contain 100 mg unit dose of DRL_RI or US-rituximab/EU-rituximab in 10 mL single-use vial or each 500 mg vial will either contain 500 mg unit dose of DRL_RI or US-rituximab/EU-rituximab in 50 mL single-use vial.

5.4 Management of Clinical Supplies

5.4.1 Packaging

Rituximab concentrate for solution for infusion will be packaged in a carton or kit. Each carton or kit will have 2 vials of 500 mg vials to achieve 1000 mg of single dose (on Day 1 and respectively on Day 15) OR 10 vials of 100 mg to achieve 1000 mg of single dose (on Day 1 and respectively on Day 15). Each carton will be packaged with a tamper-resistant seal. The sponsor must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used. Further details will be provided in the pharmacy manual.

5.4.2 Labelling

Medication labels will comply with the legal requirements of each country and be printed in local language, if required. They will supply no information about the subjects.

5.4.3 Storage

DRL_RI and US-rituximab/EU-rituximab 100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials should be stored at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. DRL_RI and US-rituximab/EU-rituximab vials should be protected from direct sunlight. Do not freeze or shake.

From a microbiological point of view, the prepared DRL_RI and US-rituximab/EU-rituximab solutions for infusion should be used immediately. Further details regarding preparation and storage of study treatments will be provided in pharmacy manual.

The investigator, or an approved representative (e.g., pharmacist), will ensure that all study treatment is stored in a secured (locked) area with restricted access, and in accordance with applicable regulatory requirements.

Study treatment should be stored in accordance with the drug label. Investigators and site staff should ensure that thermometers are working correctly, and the drug is being stored as required for proper storage of study treatments. More details will be captured in pharmacy manual. Any temperature excursions should be reported to the sponsor or sponsor designate.

Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor or sponsor designate. Once a deviation is identified, the study treatment must be quarantined and not used until the sponsor provides documentation of permission to use the study treatment.

5.4.4 Study Treatment Accountability

Records will be maintained of the delivery of study treatment to the study sites, the inventory at the study sites, the use of each subject, and the return to the sponsor.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study medication and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the study treatment specified by the IWRS and that all study medication received from the sponsor is reconciled.

5.5 Overdose Management

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Every overdose must be reported to the sponsor or sponsor's designated safety services within 24 hours of awareness, irrespective of whether the overdose was associated with an AE/SAE. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with an overdose, these should be reported in the relevant AE/SAE sections of the eCRF.

5.5.1 Medication Errors

Medication errors may result in this study from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the study treatment.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE eCRF page.

5.6 Transmission of Infectious Agents

All subjects will be provided with patient alert card with each infusion. The alert card contains important safety information for subjects regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy.

5.7 Blinding

A double-blind design is employed so that both the investigators and the subjects will be unaware of the treatment assignment during the whole study. Moreover, study center staff involved in study treatment administration and study endpoints assessments, CRO personnel, and the sponsor team including study statistician will be blinded to the treatment received. The clinical laboratories analyzing the blood/plasma samples and the concentration/incidence of anti-rituximab antibodies will also be blinded to the treatment assignment. A team from the CRO, independent to the clinical monitoring group, shall be responsible for maintaining drug accountability logs. An unblinded study coordinator or pharmacist at each site will be responsible for maintaining drug accountability as well as for dispensing. The final CSR will include all end points, after all subjects complete the Week 12 (EOS/ET) visit and the database up to the Week 12 (EOS/ET visit) has been locked. The study will be unblinded after the database up to the EOS/ET visit has been locked. The subsequent follow-up data from Week 12

to 26 will be reported as an addendum to the final CSR and for the data up to and including the Week 12 or ET visit.

5.7.1 Breaking the Blind

A subject's treatment assignment will not be broken until the EOS unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation.

The study site investigator and appropriate project team members will be authorized to access the emergency unblinding functionality within the IWRS. The system will require the user to enter an authorization key number to complete the emergency unblinding transaction. The exact description of the treatment assigned to the individual subject then will be accessible. Emergency unblinding can thus be made for any subject without affecting the double-blind nature of the study. Subject treatment information may only be accessed in the event of an emergency and out of necessity to know the identity of the allocated study treatment in order to institute appropriate therapeutic management. Should a situation arise where unblinding is urgently required (i.e., knowledge of treatment code is required to adequately manage a life-threatening situation), the investigator at that study site may perform immediate unblinding through the IWRS. If time allows, the investigator should contact the medical monitor prior to unblinding the individual subject to discuss the rationale for emergency unblinding.

In the event that emergency unblinding is performed, the investigator can view and must print the blinded confirmation document from IWRS. The investigator must record on the confirmation document printout the reason for the emergency unblinding and sign the document. The confirmation document must then be kept in a safe place until Week 26. Once a randomization code has been broken for a subject, he/she must be withdrawn from the study. The investigator must inform the medical monitor/designee in writing within 24 hours.

5.8 Treatment Compliance

Study treatment will be administered under the supervision of the investigator and site personnel. Compliance will be monitored by study personnel at the site by using the source documents and the eCRF. The site study unblinded pharmacist/authorized designee is responsible for drug preparation, the maintenance of accurate and complete dispensing and

accountability forms showing the receipt and dispensation of the study treatment. The pharmacist will also be responsible for performing accountability and reconciliation of the study treatments.

5.9 Prior and Concomitant Therapy

Medications that are considered necessary for the subject's safety and well-being may be given during the course of the study at the discretion of the investigator and must be recorded in the appropriate sections of the eCRF.

All medications taken by a subject within 1 month prior to the screening visit are regarded as **prior medication** and must be documented as such in the eCRF.

All medications still being taken by a subject at randomization and which continue to be taken during the study and medications started during the study are regarded as **concomitant medication** and must be documented as such in the eCRF.

5.9.1 Background Medication

A stable dose of weekly MTX (7.5 mg to 25 mg) and folic acid (at least 5 mg per week) that the subject is receiving are considered as background medications. Subjects have to be on a stable dose of weekly MTX (between 7.5 mg and 25 mg) for at least 4 weeks prior to randomization and during the study and folic acid (at least 5 mg per week).

Note: MTX and folic acid should be used in accordance with the guidelines specified in the local label (e.g., SmPC in the EU, US PI for the US). Folinic acid at the same dose of folic acid, can be given in place of folic acid if it is allowed by the local label. Subject should take the same folate supplementation throughout the duration of the study.

5.9.2 Other Concomitant Medication

Low-dose corticosteroids (≤10 mg/day prednisone equivalent) and non-steroidal anti-inflammatory drugs as needed are permitted concomitant medications for RA during this study.

Concomitant administration of any other experimental drug, biological medicinal products, B-cell modulating or cell-depleting biologic therapy, JAK inhibitors, anti-rheumatic drugs including DMARDs other than MTX (along with folic acid), tofacitinib, glucocorticoids used

as pre-medication other than methylprednisolone or its equivalent, or immunotherapy is prohibited during study participation.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign the ICF.

6.1 Schedule of Assessments

An overview of the protocol visits and procedures is provided in Table 14-1.

The investigator may plan unscheduled visits in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject. If any unscheduled visits happen at any time during the study, visit details/appropriate data including the reason will be collected in the eCRF.

6.1.1 Screening Period (Days -14 to 0)

Subjects will undergo a screening visit, within 14 days prior to the planned first day of study treatment. During the screening visit, subjects will be screened at the study site to confirm their eligibility for participation in the study. The investigator or sub-investigator will discuss with each subject the nature of the study, its requirements, and its restrictions. Written and signed ICF must be obtained from each subject prior to the conduct of any protocol-specific procedures.

Screening procedures and assessments will be as follows:

The proposed chronological order of the assessments below should be followed.

1. Obtain written informed consent from the subject in accordance with local regulations.
2. Register screening of the subject.
3. Review subject eligibility (inclusion and exclusion criteria). Any questions regarding subject eligibility can be addressed to the medical monitor.

4. Document medical and surgical history (includes full history of RA and other rheumatic diseases, including their related procedures, all ongoing conditions at the time of screening, all major surgical procedures [i.e., those involving opening of cavities or epidural or general anesthesia] with their reason, and any past event or procedure considered relevant by the investigator as well as any minor event occurring in the month prior to screening).
5. Document subject demographics.
6. Clinical assessments will include the following: physical examination (including height and weight), vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
7. Serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) to be performed for WOCBP. Female subjects with documented history of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, medically confirmed ovarian failure, or screening follicle-stimulating hormone (FSH) test demonstrating postmenopausal status are exempted from pregnancy testing.
8. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed.
9. Tuberculosis screening (if required by local regulation or practice).
10. Viral disease screening: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).

    Note: For HBcAb, site is requested to perform HBcAb IgG and HBcAb IgM. If any of these 2 results is positive, then the subject will be considered as screen failure.
11. Twelve-lead electrocardiogram (ECG).
12. Assess AE(s).
13. Prior and ongoing medications.
14. Serum Immunoglobulin (IgG and IgM)

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened at the investigator's discretion, following discussion with the sponsor designee medical monitor. Subjects not included in the study due to latent TB (in the locations where

TB screening is required) will also require rescreening after appropriate treatment has been administered per local guidance.

6.1.2 Treatment Period (2 Weeks)

Subjects will attend study visits at Week 0 (Day 1) + 1 day and Week 2 (Day 15) + 1 day.

Samples for the evaluation of ADA, including titer and NAb (immunogenicity assessments), will be obtained before the administration of study treatment on Day 1 and Day 15.

In the description of evaluations below:

Study Day 1 (Week 0, Baseline Visit)

Eligible subjects will return to the study site for the baseline (Week 0, Day 1) visit. Subjects must satisfy all inclusion/exclusion criteria in order to be eligible for randomization.

Baseline procedures and assessments should be conducted in chronological order as follows:

1. Re-review subject eligibility (inclusion and exclusion) criteria to ensure that the subject continues to be eligible for inclusion into the study. Any questions regarding subject eligibility can be addressed to the medical monitor.
2. Clinical assessments will include the following: physical examination, vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
3. Urine pregnancy test for WOCBP.
4. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed (see Section 6.3.4 for the list of clinical laboratory assessments).

   Note: Viral disease screening (HBsAg, HBcAb, HCV, HIV), and serum IgG and IgM and TB screening will not be repeated on Day 1 of the study. Clinical laboratory assessments scheduled on Day 1 can be performed 1 day prior to dosing.

   Note: For HBcAb, site is requested to perform HBcAb IgG and HBcAb IgM. If any of these 2 results is positive, then the subject will be considered as screen failure.
5. Randomize the subject in accordance with the IWRS.

6. Collect plasma samples for immunogenicity assessments prior to administration of study treatment.
7. Collect a time-matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.
8. Study treatment administration and observation for at least an hour post infusion.
9. Assess AE(s).
10. Record concomitant medication(s).

Study Day 15 (Week 2 + 1 Day)

The procedures and assessments are as follows:

1. Clinical assessments will include the following: physical examination, vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
2. Urine pregnancy test for WOCBP.
3. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed.
4. Collect plasma samples for immunogenicity assessments prior to administration of study treatment.
5. Collect a time-matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.
6. Study treatment administration and observation for at least an hour post infusion.
7. Assess AE(s).
8. Review concomitant medications.

6.1.3 Follow-Up Period (10 Weeks)

Week 4 ± 7 Days

The procedures and assessments for Week 4 ± 7 days are as follows:

1. Clinical assessments will include the following: physical examination (including weight), vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
2. Urine pregnancy test for WOCBP.
3. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed.
4. Collect plasma samples for immunogenicity assessments.
5. Collect a time-matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.
6. Assess AE(s).
7. Review concomitant medications.

Week 8 ± 7 Days

The procedures and assessments for Week 8 ± 7 days are as follows:

1. Clinical assessments will include the following: physical examination (including weight), vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
2. Urine pregnancy test for WOCBP.
3. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed.
4. Collect plasma samples for immunogenicity assessments.
5. Collect a time-matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.
6. Assess AE(s).

7. Review concomitant medications.

6.1.4 End of Study/Early Termination Visit (Week 12 ± 7 Days)

Subjects who complete the study or discontinue from the study at any time will attend an EOS/ET visit.

The EOS/ET assessments are as follows:

1. Clinical assessments will include the following: physical examination (including weight), vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).
2. Serum pregnancy test (β-hCG) for WOCBP. Female subjects with documented history of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, medically confirmed ovarian failure, or screening FSH test demonstrating postmenopausal status are exempted from pregnancy testing.
3. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed.
4. Twelve-lead ECG.
5. Collect plasma samples for immunogenicity assessments.
6. Collect a time-matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.
7. Assess AE(s).
8. Review concomitant medication(s).

6.1.5 Additional Follow-Up Visit (Week 26)

The following assessments will be performed at Week 26:

1. Clinical assessments will include the following: physical examination (including weight), vital signs measurement (seated BP, heart rate, respiration rate, and oral body temperature).

2. Serum pregnancy test for WOCBP. Female subjects with documented history of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, medically confirmed ovarian failure, or screening FSH test demonstrating postmenopausal status are exempted from pregnancy testing.
3. Clinical laboratory assessments: a blood sample will be taken for hematology (especially absolute neutrophil count) and biochemistry; urinalysis will also be performed.
4. Twelve-lead ECG.
5. Assess AE(s).
6. Review concomitant medications.

6.2 Immunogenicity Endpoint

The immunogenicity endpoint is the incidence of ADA, including titer and NAb.

6.2.1 Immunogenicity Sampling

Blood samples for detection of ADA (including NAb) will be collected prior to initiation (preferably within 30 minutes) of infusion of study treatment on Day 1 and Day 15 and then on visits at Weeks 4, 8, and 12 (EOS/ET) as specified in Table 14-1 and Section 6.1.

Whole blood samples (approximately 10 mL) will be collected and processed to obtain approximately 4 mL of plasma for ADA (including titer and NAb) detection at each time point. Samples should be processed per detailed instructions in the laboratory manual for collection by the central laboratory. The samples will be shipped to laboratories for ADA titer and NAb analysis by the central laboratory as detailed in the laboratory manual.

Along with the immunogenicity sample, a time-matched blood sample (approximately 5 mL) will be collected for the estimation of rituximab concentration. The evaluation of the samples will be performed to interpret safety and/or immunogenicity data appropriately, if needed.

The central laboratory shipment address and assay laboratories contact information will be provided to the investigator prior to or during the initiation of the study.

Further details on sample collection, processing, and shipment are provided in full in the laboratory manual.

6.2.2 Immunogenicity Assay

Immunogenicity samples will be analyzed by designated analytical laboratory(ies) using validated methods. Analysis of ADA samples will follow a tiered approach of screening, confirmation, and titer determination. Samples that are confirmed positive for ADA will be further tested for titer and NAb using validated assays.

Immunological testing in human subjects will involve a multi-tiered approach as outlined below:

Tier I Screening Assay: All the clinical samples for immunogenicity assessment will be subjected to a screening assay. The methodology is based on the principle of capture of the ADA by the drug and detection by biotin-labelled drug, using ELISA. The test methodology may be modified after the method validation is completed. During method validation, an assay cut point is statistically determined. The samples that show a response equal to or above the pre-determined screening cut point will be called as "screening positive" and the ones that show a response below the assay cut point will be called as "negative".

Tier II Confirmation Assay: All the clinical samples that are "screening positive" will be subjected to a confirmation assay. This will involve the inhibition of the response seen in the screening assay with high concentration of drug. The assay format is an adaptation of the screening assay, where the samples are spiked with phosphate-buffered saline or drug and incubated for 1 hour at 37°C prior to evaluation according to the screening assay procedure. The samples that show a response equal to or above the pre-determined confirmatory cut point will be called as "confirmed positive" and the ones that show a response below the assay cut point will be called as "negative".

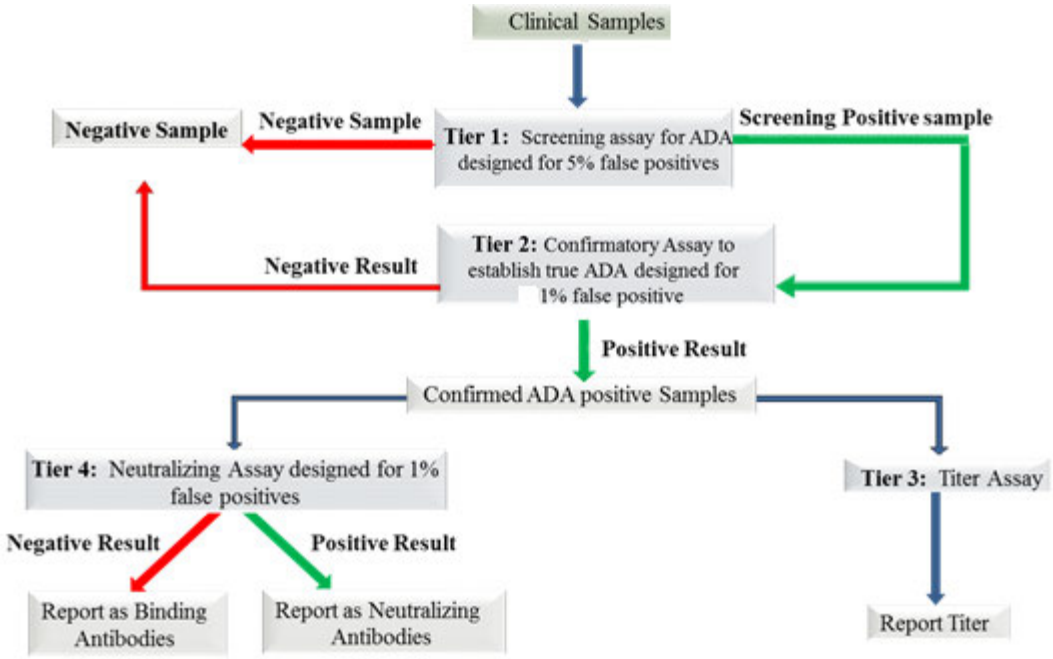
Tier III Titer Determination: It is the semi-quantitative assay where titers of the confirmed ADA-positive samples will be evaluated with respect to a previously established titer cut point. During the clinical sample analysis, serial 2-fold dilutions of confirmed positive samples will be performed and the reciprocal of the dilution able to yield a response at or above the titration cut point will be reported as the titer of the ADAs.

Tier IV Neutralizing Antibodies Assay: This is based on the principle that any 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. This is based on the mechanism

of action of the drug (rituximab) and is used to characterize the neutralizing activity of the confirmed ADA-positive samples. Rituximab induces CDC. The ability of the ADA to neutralize the CDC activity of rituximab will be assessed in a cell-based assay. This assay is developed and will be validated prior to clinical sample analysis. This assay is a characterization of the confirmed ADAs.

The diagrammatic representation of the immunogenicity assessment of rituximab in the clinical study is shown in Figure 6-1.

Figure 6-1: Flow Diagram for the Evaluation and Characterization of Anti-Drug Antibodies



Abbreviation: ADA, anti-drug antibody.

Comprehensive information regarding validity, specificity, and sensitivity of immunogenicity assays used in this study will be provided in a separate report.

6.3 Safety Assessments

The safety endpoints of this study are as follows:

- Incidence of TEAEs and SAEs.

- Incidence of anaphylactic reactions, hypersensitivity reactions, and IRRs.

Other safety endpoints will include the following:

- Clinical laboratory parameters
- Vital signs
- Twelve-lead ECG
- Physical examination

Definitions

Infusion-related Reactions

Infusion-related reactions are defined as a group of acute reactions to the allergen (or therapeutic protein for this study) that occur during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include the following: allergic reaction (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritis/itching, rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, tumor pain (onset or exacerbation of tumor pain due to treatment), urticaria (hives, welts, wheals), and vomiting (Doessegger L and Banholzer ML 2015).

Hypersensitivity Reactions

Any AE, which occurs 24 hours of completion of infusion and with clinical or clinical laboratory (if performed) features suggesting an immunoallergic mechanism and without any other supported alternative explanation and not fulfilling the provided definition of anaphylactic reaction.

Hypersensitivity reactions to biologic agents are less common than standard IRRs. Although some clinical signs and symptoms are more unique to hypersensitivity reactions, many are similar. Hypersensitivity and standard IRRs can have gastrointestinal symptoms, dyspnea, flushing, pruritus, and back pain. Symptoms that are more suggestive of a hypersensitivity reaction would include urticaria, wheezing, frequent coughing, and anaphylactic symptoms (Khan DA 2016).

Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria (criteria of the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network), which will be applied for diagnosing anaphylaxis (Sampson HA 2006) are fulfilled based on the principal investigator's discretion or clinical evaluation:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow or hypoxemia).
    b. Reduced BP or associated symptoms of end organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
    a. Involvement of the skin mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula).
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that subject (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (this study is going to be conducted in adult subject population, hence this criterion will not be applicable here).
    b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Note: Above differentiating features of IRRs, hypersensitivity and anaphylaxis are recommendations based on the literature (Doessegger L and Banholzer ML 2015, Khan DA

2016, Sampson HA 2006). The investigator should use his/her clinical judgment to document it as IRRs and/or hypersensitivity reactions and/or anaphylaxis.

The timing and frequency of safety assessments are described in Section 6.1.

6.3.1 Adverse Events

6.3.1.1 Definitions

The definitions for AEs, SAEs, and TEAEs are given below. It is of the utmost importance that all site personnel involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

6.3.1.1.1 Adverse Event/Reaction

An AE is defined as any untoward medical occurrence in a subject, or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

Any relevant observations made at the screening visit (prior to signing the ICF) are to be recorded as a preexisting condition; an AE will only be recorded if there is a worsening of the preexisting condition during study conduct with regards to nature, severity, or frequency.

An ADR is an untoward and unintended response to a study treatment related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments meant to suggest a causal relationship.

A pre-treatment event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

Serious Adverse Event

An SAE is defined as an AE that results in 1 of the following outcomes:

- Results in death.

  Death is not an AE/SAE itself, but an outcome. The cause of the death is an AE, which resulted in death.

- Is life-threatening.

  Life-threatening means that the subject was at immediate risk of death at the time of the SAE, it does not refer to an SAE that hypothetically might have caused death if it were more severe.

- Requires in-subject hospitalization or prolongs existing hospitalization (This does not include prolonged hospitalization for study purposes).

  Hospitalization is defined as at least 1 overnight formal admission into hospital, usually to perform additional tests, provide treatment that it is not possible to provide at home and/or to allow specific monitoring of the subject due to their unstable medical condition. Current hospitalization due to preplanned hospitalizations (known already prior to signing the ICF) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalization due to unplanned complications. Following the initial discharge from hospital, subsequent hospitalizations are to be considered an SAE. "Social" hospitalization, defined as administrative impossibility to discharge the subject is not necessarily an SAE. Complications that occur during hospitalization are AEs unless they would qualify as an SAE for any of the above criteria. If the complication delays the subject's release from hospital, then the AE becomes an SAE. Hospitalizations due to diagnostic procedures which are not performed due to an AE are not regarded as SAE.

- Results in persistent or significant disability/incapacity.

  The term significant disability refers to any condition that impairs physical/psychological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction as development of heart failure, liver insufficiency, or pulmonary fibrosis.

- Is a congenital anomaly/birth defect.

- Is an important medical event.

  Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment they may jeopardize the subject or the subject may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

6.3.1.1.2 Treatment-Emergent Adverse Event

Treatment-emergent AEs are defined as any AE occurring or worsening on or after the first dose of study medication.

6.3.1.2 Recording of Adverse Events

Any relevant observations made at the screening visit (prior to signing the ICF) are to be recorded as a preexisting condition. For the purposes of this study, any detrimental change in the subject's condition, after signing the ICF and up to completion of the 26-week study period, should be considered as a TEAE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, action taken with the study treatment, and the outcome. If the severity of the event changes, the event with the highest severity will be recorded.

Serious AEs and TEAEs will be recorded starting after signing of the ICF. All SAEs and AEs have to be recorded, whether or not considered causally related to the study treatment or to the study procedure(s).

All ongoing nonserious AEs should be followed up until resolution or stabilization or the EOS/ET visit, whichever occurs first, with the exception of any ongoing treatment-related nonserious AEs that should be followed until that AE is stabilized, resolved, or, in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying condition.

All ongoing SAEs should be followed up until resolution or stabilization/or until a pre-defined outcome is reached.

Note: Outcome information received on on-going SAE beyond the date of data base lock, will be captured in safety database and reported as follow-up report in the form of individual case safety report.

At any time after the additional follow-up visit, if an investigator learns of an SAE that can be reasonably related to study treatment, he/she should promptly notify the sponsor/designee.

6.3.1.3 Assessment of Severity

Whenever possible, the intensity of clinical AEs will be graded according to National Cancer Institute (NCI) CTCAE (Version 5.0 or any latest version) grading system. Adverse events not listed in the NCI CTCAE grading system will be graded on a 5-point scale (mild, moderate, severe, life-threatening, and death) as described below, and reported in detail as indicated on the eCRF.

Severity Grading for Adverse Events Listed in NCI CTCAE (Version 5.0 or any Latest Version):

- **Grade 1: Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2: Moderate**: minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL) (Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- **Grade 3: Severe:** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4: Life-threatening:** life-threatening consequence; urgent intervention indicated.
- **Grade 5:** death related to AE.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it meets 1 of the criteria for SAEs, listed in Section 6.3.1.1.1.

6.3.1.4 Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report in the eCRF. **However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data via eCRF.** The investigator may change his/her opinion of causality in light of follow-up information and change the assessment in the eCRF, which will trigger an alert to the sponsor's designated safety services. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The following "binary" decision choice will be used by the investigator to describe the causality assessment:

- Reasonable possibility of relatedness (i.e., related)
- No reasonable possibility of relatedness (i.e., not related)

The term "reasonable possibility of relatedness" is meant to convey, in general, that there is enough evidence or argument to suggest the causal relationship. The investigator should consider the following before reaching a decision on causality assessment:

- Time relationship between study treatment intake and event's onset;
- Dechallenge;
- Rechallenge;
- Medical history;
- Study treatment;
- Mechanism of action of study treatment;
- Class effect;

- Concomitant treatments in use;
- Withdrawal of study treatment;
- Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study medication or concomitant medication;
- Protocol-related process.

Action taken with study treatment due to the AE:

- Dose not changed;
- Drug interruption;
- Drug withdrawn;
- Unknown;
- Not applicable.

Outcome:

Each single AE must be rated by choosing 1 of the following:

- Recovered/resolved;
- Recovering/resolving;
- Not recovered/not resolved;
- Recovered with sequelae/resolved with sequelae;
- Fatal;
- Unknown.

Note: If an event is stabilized per opinion of the investigator, then outcome option of "Not recovered/not resolved" to be selected in drop down list of outcome in eCRF. However, in AE/SAE description free filed of eCRF, investigator has to mention the event is assessed as "Stabilized" on a given date.

The investigator and the sponsor (or sponsor's designee) will review each SAE report and the sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the sponsor (or sponsor's designated agent) will evaluate the

expectedness according to the reference document (IB or SmPC or PI). Based on the investigator and sponsor's assessment of the event, a decision will be made concerning the need for further action.

6.3.1.5 Reporting of Serious Adverse Events

Investigators and other site personnel must inform as appropriate to the sponsor's designated safety services of any SAEs that occur (whether or not attributable to the study treatment) in the course of the study within 1 day (24 hours) (i.e., immediately but no later than the end of the next calendar day) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported by the investigator to the sponsor's designated safety services within the same time frames.

If a nonserious AE becomes serious, this and other relevant follow-up information must also be provided to sponsor's designated safety services within 24 hours as described above.

All SAEs must be reported, whether or not considered causally related to the study treatment or study procedure(s). All SAEs will be recorded in the eCRF; paper forms will be used as a back-up only if the eCRF is unavailable. The investigator is responsible for informing the IEC/IRB of the SAE per local requirements.

Source documents relevant for the SAE must be reported upon request by sponsor's designated safety services. Due to data protection laws, please ensure redaction of the subject's identifiers (name, address, and date of birth [only year of birth is allowed]) from the discharge summary, autopsy report, laboratory reports, and any other documents/reports when sending to the sponsor's designated safety services.

The completed and signed SAE or pregnancy report form must be attached to the email. A notification email of the event describing it in the email text is not sufficient.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial SAE report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report form. Minimum criteria are identifiable subject (number), a suspect product (i.e., study treatment or concomitant medication), an identifiable reporting source (investigator/study site identification), and an event or outcome that can be identified as

serious. The investigator may change his/her opinion of causality in the light of follow-up information, amending the SAE report form accordingly. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements for SAEs.

When an SAE is discovered by the site or is identified by a clinical research associate during site visits, SAEs will be entered by the site members into the eCRF, which contains specific questions for events regarded as serious. The designated personnel will receive the alert through automated email notification.

The sponsor/designee representative will work with the investigator to compile all the necessary information and ensure that the appropriate sponsor representative receives a report within 1 calendar day (24 hours) for all fatal and life-threatening cases and within 5 calendar days for all other SAEs per the applicable local regulatory guidelines. All SAEs and follow-up information on the SAEs are to be reported to CI Pharmacovigilance in 24 hours regardless of seriousness criteria.

Prompt notification of SAEs to the sponsor/designee, as described above, is essential so that regulatory requirements and ethical obligations to the subjects involved in the study can be met. The investigator is responsible for informing the IEC/IRB of the SAE per local requirements. Unblinding relating to suspected unexpected serious adverse reactions (SUSARs) (if required) will be performed by the sponsor/designee in accordance with standard operating procedures (SOPs), working practice documents, and documented study-specific procedures.

6.3.1.6 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study intervention, and unexpected (SUSAR) has additional reporting requirements as described below.

- If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IEC/IRB will be notified within 7 calendar days after the sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IEC/IRB will be notified within 15 calendar days after the sponsor learns of the event.

The sponsor's designated safety services will also provide periodic and annual safety updates to the regulatory authorities, IEC/IRB responsible for the study, and investigators per local regulations. These updates will include information on SUSARs and other relevant safety findings.

6.3.2 Abnormal Laboratory Values/Vital Signs Measurements/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as an AE/SAE if any 1 of the following criteria is met:

- Result is associated with signs/symptoms;
- Requires additional diagnostic testing and/or interventions;
- Leads to a change in dose, discontinuation of, or interruption to the study treatment.

Repeats of an abnormal test result without any of the above criteria do not constitute an AE.

Any test result determined to be an error is not required to be reported as an AE.

6.3.3 Deaths

Should a death occur within the study period, an AE form and an SAE report form should be completed, detailing the AE that resulted in the death (Note: death is an outcome, not an event). The SAE must be reported to the sponsor or the sponsor's designated safety services within 24 hours as described in Section 6.3.1.5.

Expedited reporting is determined by the CRO depending on the information provided by the site, e.g., AEs that are fatal/life-threatening and related to the study drug would be considered as expedited and reported to regulatory authorities and IEC/IRB within 7 calendar days. Adverse events with any other seriousness criteria and relatedness would be reported to regulatory authorities and IEC/IRB within 15 calendar days.

6.3.4 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed as indicated in Table 14-1. Hematology, biochemistry, and urinalysis will be conducted at the following visits: screening, on Day 1, Day 15, and at Weeks 4, 8, 12 (EOS/ET), and 26 (additional follow-up). Serum pregnancy test will be conducted at screening, Week 12 (EOS/ET), and Week 26 (additional follow-up) visits. Urine pregnancy test will be conducted on Day 1 prior to randomization, and Day 15 (before dosing), at Week 4 and Week 8 visits.

Hematology, biochemistry, urinalysis, and pregnancy tests will be performed by the local laboratory according to local practice. Local laboratory normal ranges will be collected prior to first subject first visit at each site and provided to data management via the study team. Laboratory results collected from the local laboratory should be entered in the eCRF by the investigator. The following parameters will be assessed:

- Hematology: red blood cell count, white blood cell count with differential count and percentages (including absolute neutrophil count), total hemoglobin, hematocrit, platelet count, and prothrombin time.
- Biochemistry: creatinine, blood urea nitrogen, fasting serum glucose, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, albumin, chloride, calcium, phosphorous, uric acid, total protein, sodium, and potassium.
- Serum IgG and IgM.
- Urinalysis (specific gravity, pH, protein, glucose, and blood).
- Pregnancy test: serum β-hCG test and urine pregnancy test for WOCBP.
- Serum FSH for postmenopausal women.

Note: Per CTFG 2014 guidelines, a postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in postmenopausal women is to be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Hence, in such cases or in some other cases in which if menopausal status is difficult to confirm, then investigators are advised to investigate further to rule out childbearing potential along with serum FSH.

Blood and urine collection and blood sample preparation will be performed according to procedures from the local laboratories.

6.3.5 Physical Examination

Complete physical examinations will be performed as indicated in Table 14-1. The following parameters and body systems will be examined and any abnormalities described: weight, height (at screening visit only), general appearance, skin (e.g., presence of rash), head, eyes, ears, nose, throat, lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam for the presence of peripheral edema, abdominal (palpation and auscultation), and neurologic (mental status and motor and sensory function). The physical examination must include a thorough assessment of the lymph nodes, liver, and spleen. The genitourinary system may be excluded unless there are signs or symptoms involving that system. Any clinically significant changes from the screening visit after initial dosing with study treatment should be recorded as AEs.

6.3.6 Vital Sign Measurements

Vital signs, including heart rate, seated BP, respiration rate, and oral body temperature, will be measured as detailed in Table 14-1 and in the event of an IRR.

Blood pressure will be measured in the subject's arm and recorded to the nearest mmHg after the subject has been seated quietly for at least 2 minutes. The same arm and position should be used throughout the study, using an appropriate cuff size. All BP readings should be measured after resting for at least 5 minutes. When the timing of these measurements coincides with blood collection, the BP and heart rate should be obtained first.

Vital signs are to be obtained prior to each study treatment infusion, every 30 minutes (± 5 minutes) during infusion, at the end of infusion, and as clinically indicated. In the event of hypersensitivity reaction, vital signs should be obtained at additional time points until recovery per investigator judgment.

6.3.7 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed as indicated in Table 14-1 under medical supervision. Before recording, subjects should be resting in a quiet supervised setting with minimal

stimulation (e.g., no television, loud music, and computer games) and lie in a resting position for 10 minutes before ECG recording.

All ECGs are to be read locally with local ECG equipment by an appropriately qualified and experienced ECG reader at the study site.

Corrected QT interval (QTc) value will be calculated using the Fridericia formula ($QTc = QT/(RR^{-1/3})$), QTc should be expressed in milliseconds, the provided formula assumes QT also in milliseconds and RR in seconds. The QTc interval will be automatically calculated. In the case of clinically significant ECG abnormalities, the investigator should report these as an AE if not due to a preexisting condition or if a preexisting condition worsens in frequency or intensity.

6.3.8 Viral Disease Screening

Subjects will be tested for HIV, hepatitis B, and/or hepatitis C to determine eligibility at screening visit.

HBsAg, HBcAb, HCV, and HIV are to be determined by each site's local laboratory.

Note: For HBcAb, site is requested to perform HBcAb IgG and HBcAb IgM. If any of these 2 results is positive, then the subject will be considered as screen failure.

6.4 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study treatment will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented. Follow-up should be done up to delivery and after the examination of the newborn a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the newborn.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as an AE. All outcomes of pregnancy must be reported to the sponsor on a pregnancy outcomes report form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to the sponsor or sponsor's designated safety services using the reporting details provided in Section 6.3.1.5 within 24 hours of awareness.

6.5 Blood Loss During the Study

For the safety evaluation, approximately 10 mL of blood will be withdrawn from the subjects at each time point. A total of approximately 145 mL of blood will be collected per subject during the study for immunogenicity, for estimation of rituximab concentration, and safety evaluation as mentioned in Table 6-1.

Table 6-1: Blood Loss During the Study

Time Points	Safety Evaluation (Laboratory)	ADA and NAb Evaluation	For Estimation of Rituximab Concentration (Approximately)	Total Volume of Blood Loss
Screening	10 mL	-		10 mL
Week 1/Day 1	10 mL	10 mL	5 mL	25 mL
Week 2/Day 15	10 mL	10 mL	5 mL	25 mL
Week 4	10 mL	10 mL	5 mL	25 mL
Week 8	10 mL	10 mL	5 mL	25 mL
Week 12	10 mL	10 mL	5 mL	25 mL
Week 26	10 mL	-	-	10 mL
Total volume of blood loss	70 mL	50 mL	25 mL	145 mL

Abbreviations: ADA, anti-drug antibody; NAb, neutralizing antibody.

Note: For safety evaluation, more than 10 mL of blood can be withdrawn based on the site/local laboratory practice and will not be considered as a deviation.

7 Statistical and Analytical Plan

7.1 Sample Size Calculations

CI [redacted]

CI [redacted]

7.2 Analysis Sets

The safety population will include all subjects who are randomized and receive at least 1 dose of study treatment.

Immunogenicity population will include all subjects with at least 1 post-dose ADA assessment result available.

Analyses of safety parameters will be based on the safety population, and immunogenicity parameters (ADA and NAb) will be based on the immunogenicity population.

7.3 Description of Subgroups to be Analyzed

Immunogenicity and key safety parameters will be presented overall and by region, as appropriate.

7.4 Statistical Analysis Methodology

7.4.1 General Principles

The statistical analysis will be performed using SAS Version 9.4 or later.

The immunogenicity and safety data will be analyzed descriptively. All individual data as well as results of statistical analyses, whether explicitly discussed in the following sections or not, will be presented in individual subject data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, and maximum. Categorical variables will be displayed by means of frequency tables including percentages.

Baseline is defined as the last non-missing pre-dose assessment. Overall summaries and analyses will be performed based on data pooled from all sites.

A SAP will be prepared and finalized before the clinical study database is closed.

7.4.2 Missing Data

All efforts will be made to ensure that all values are populated for start and stop date of AE/concomitant medication and severity and causality of AE. In case of any missing or partial dates for AEs, concomitant medication, and any other dates required for analysis still exists, then those will be imputed in an appropriate conservative way. For AEs, missing severity and relationship with treatment, if any, will also be imputed in an appropriate conservative way. Further details will be described in the SAP.

Other missing values will not be imputed, unless otherwise specified in each analysis section.

7.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be analyzed in a descriptive fashion and results will be presented overall and by treatment arm.

7.4.4 Subject Disposition

The following will be summarized (overall and by treatment arm where applicable):

- Subjects screened.
- Subjects randomized.
- Subjects in the safety analysis set.
- Subjects completing the study/withdrawing early (including withdrawal reason).

7.4.5 Immunogenicity Analysis

The immunogenicity endpoint of this study is the incidence of ADA, including titer and NAb.

Immunogenicity data (ADA and NAb) will be summarized and analyzed descriptively for each scheduled protocol assessment time point by treatment arm and overall.

Further details of the analysis will be described in the SAP.

7.4.6 Safety Analysis

The safety analysis will be based on the safety population and will be analyzed according to the treatment they actually received. Detail methods will be described in the SAP.

The safety endpoints are as follows:

- Incidence of AEs.
- Incidence of anaphylactic reactions, hypersensitivity reactions, and IRRs.

Other safety endpoints will include the following:

- Clinical laboratory parameters
- Vital signs
- Twelve-lead ECG
- Physical examination.

Treatment-emergent AEs will be described using descriptive statistics and coded according to the Medical Dictionary for Regulatory Activities (MedDRA), system organ class and MedDRA preferred term, graded according to CTCAE (Version 5.0 or any latest version), by treatment arm and overall. TEAEs observed, will be summarized separately by treatment arm. Treatment-related TEAEs and SAEs, TEAEs leading to study discontinuation, and deaths will be also summarized by treatment arm.

Incidence of anaphylactic reactions, hypersensitivity reactions, and IRRs will be summarized by treatment arm and overall.

Clinical safety laboratory data will be presented by treatment arm and overall. For each visit, the actual result and the change from baseline will be presented. Shift tables for values outside the clinical normality status will be presented as appropriate.

Otherwise, safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. For continuous measurements (laboratory and vital signs data), change from baseline will be additionally summarized by treatment arm and visit.

Subject listings will be produced for all safety endpoints.

7.4.7 Interim Analyses

There will be no interim analysis in this study.

8 Quality Control and Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

8.1 Case Report Forms/Source Data Handling

An eCRF is required and should be completed for each included subject. The investigator shall be provided with standardized eCRF and shall ensure that all data from subject visits are promptly entered into the eCRF in accordance with the specific instructions given.

The investigator must maintain source documents at the study site to support the data entered into the eCRF. Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study, such as laboratory reports, edges, consultation reports, complete medical history, and physical examination reports.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRF must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRF is true.

8.2 Data Management

A data management plan will be prepared before data collection initiates. The data management plan will describe all study specifics functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the electronic data capture system and followed up for resolution. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. Data collection and entry is the

responsibility of CRO that will develop a quality control plan to assure that the data entered in the eCRFs reflects the source documents maintained on site. Entered data will be verified by the clinical monitor/data manager/designee who will query the site for potential discrepancies. The site investigator or designee will be responsible for resolution of queries. Coding of medical history, AEs, and concurrent conditions will be performed using latest version of MedDRA and coding of prior and concomitant medications and therapies will be performed using the current version of World Health Organization Drug (WHODRUG) Dictionary. The eCRFs and any supporting documentation should be available for retrieval or review at any given time.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Investigative site personnel will enter subject data into the electronic data capture system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable CI standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

After database lock, each investigator will receive a compact disc/digital versatile disc (DVD) with portable document format (PDF) files for the subjects enrolled at their site and the sponsor will receive a Master DVD of all project data. These files will contain all of their site specific eCRF data as entered into Medidata Rave® for the study, including full discrepancy and audit history. The Medidata Rave database will be stored by Medidata. In all cases, subject initials will not be collected or transmitted to the sponsor. Additionally, a compact disc read-only memory copy of all of the study site's data from the study will be created and sent to the sponsor for storage.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH Harmonised Tripartite Guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with FDA regulations (Code of Federal Regulations [CFR], Sections 312.50 and 312.56) and with ICH GCP (Committee for Medicinal Products for Human Use [CHMP] 135/95).

9.3 Subject Information and Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering

the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject, after the receipt of detailed information on the study.

All ICFs must be available in the local languages required at the site and include subject information sheets/brochures that outline the study procedures. All ICFs must be signed and dated by the subject.

For subjects who are unable to read and write, the subject information sheet and ICF should be read to the subject in his/her native language in the presence of an impartial witness who is literate and not affiliated with the study. The subject having understood the information given to him/her in the presence of an impartial witness will thumbprint the ICF and the same will be countersigned by the impartial witness. If the subject cannot read, then an impartial witness will witness and attest the entire consent process and will be required to sign the consent form. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

The investigator is responsible for ensuring that informed consent is obtained from each subject, along with their signatures and dates on the informed consent document, prior to the performance of any protocol procedures including the administration of study drug. The investigator will provide each subject with a copy of the signed and dated consent form while the originals will be retained in the investigator's records.

The consent documents to be used for the study shall include all the elements of informed consent as outlined in the applicable SOP(s), applicable regulatory requirements, and be reviewed and approved by the appropriate IEC/IRB prior to use.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all subjects subsequently enrolled in the study as well as those currently participating in the study.

Note: Sites are advised to follow local or country-specific guidelines while obtaining consent from the subject.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, the US FDA, local regulatory(ies), or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor/CRO a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor CRO is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol.

10.4 Study Conduct

Dr. Reddy's Laboratories S.A./CRO shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non evaluable.

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC, and to any other regulatory (if required by local regulatory and laws) according to the timeline and methods outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Records Retention

To enable evaluations and/or audits from regulatory authorities or sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the clinical study agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), sponsor and/or CRO should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or to an independent third party arranged by the sponsor. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain sponsor's written permission before disposing of any records, even if retention requirements have been met.

10.8 Publications

The sponsor shall retain the ownership of all data. When the study is complete the sponsor shall arrange the analysis and tabulation of data. A CSR (Section 11.4) shall then be prepared, which may be used for publication, presentation at scientific meetings, or submission to regulatory authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.

11 Study Management

11.1 Monitoring

11.1.1 Monitoring of the Study

The investigator shall permit the site monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator shall access medical records for the monitor in order that entries in the eCRF may be verified. The investigator, as part of his/her responsibilities, is expected to cooperate with the sponsor/CRO in ensuring that the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until such time that a visit, or with the agreement of the sponsor, or attendance at the investigator meeting, has been made by a sponsor/CRO monitor to conduct a detailed review of the protocol and eCRF.

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

Note: Due to COVID-19 pandemic, provisions of remote monitoring have been added in the protocol (Section 3.2, Study Conduct during the COVID-19 Pandemic).

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Protocol Amendments

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/competent authorities, in accordance with local legal requirements. The sponsor/authorized CRO representative must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study. Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, the same needs to be promptly reported to the sponsor or its designee and the IEC/IRB and must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the CRO and/or from sponsor, and receive IEC/IRB/competent authority approval prior to implementation (if appropriate). In the United States: Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug application under which the study is being conducted.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.2.2 Protocol Deviations/Violations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is non-adherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include non-adherence to inclusion/exclusion criteria or non-adherence to FDA regulations or ICH GCP guidelines, and may lead to the subject being withdrawn from the study (Section 4.2).

All deviations from the approved protocol must be documented and notified to the sponsor/CRO at the earliest. The investigator should not deviate from the protocol, except for subject safety reasons, in which case the deviation must be reported to the sponsor/CRO immediately. The sponsor will not assume any resulting responsibility or liability from unapproved deviations. The investigator, according to applicable regulations and the IRB/IEC's established procedures, will inform the IRB/IEC of protocol deviations.

All instances where the requirements of the study protocol are not complied with, investigator/designee will file the protocol deviation and the same will be captured in a protocol deviation/violation log. Corresponding subjects may be withdrawn from the study at the discretion of the sponsor/designee. Deviations from the study protocol should not be made other than as part of a protocol amendment. An amendment must be agreed upon by the sponsor, but not implemented until written IEC/IRB approval is obtained, except where necessary to eliminate an immediate hazard to study subjects or when the change(s) involves only logistical or administrative aspects. Protocol deviations/violations and the reason why they occurred will be documented in the CSR.

11.3 Study Termination

Although Dr. Reddy's Laboratories S.A. has every intention of completing the study, Dr. Reddy's Laboratories S.A. reserves the right to discontinue the study at any time for clinical or administrative reasons.

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSR is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSR in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports.

Data until Week 12 will be analyzed and reported in the final CSR after all subjects complete Week 12 visit (EOS/ET). The subsequent follow-up data from Week 12 to Week 26 will be reported as an addendum to the final CSR and for the data up to and including the Week 12 or ET visit.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, the sponsor will provide the investigator with the full summary of the study results.

12 Financing and Insurance

The sponsor shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. If a subject incurs a study-related injury, the subject may be treated (and other necessary measures taken) at the study site and/or another medical institution. If it is necessary to compensate for the treatment, the sponsor will cover the cost. The sponsor shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, the sponsor may refuse or restrict the payment of the compensation:

1. A serious GCP or protocol deviation by the investigator or sub-investigator (except deviation medically necessary to avoid an immediate hazard to the study subjects).
2. Intentional act or negligence on the part of the investigator or sub-investigator or malpractice thereby.
3. Injury caused by unlawful act or delinquency of a third party.
4. Injury caused by intentional act or negligence of the subject.

If compensation becomes necessary for a study-related injury, the site will promptly notify the sponsor and will cooperate with the sponsor and its insurer (or their legal representatives) in their handling thereof.

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14 Appendices

14.1 Appendix 1: Schedule of Events

Table 14-1 Schedule of Events

Study Period	**Screening Visit Days -14 to 0**	**Treatment Visit**		**Follow-Up Visits**		**EOS/ET[a] Visit**	**Additional Follow-up Visit[m]**
Study Week		**0 (Day 1)**	**2 (Day 15)**	**4**	**8**	**12**	**26**
Visit Window		**+1 day**	**+1 day**	**±7 days**			
Informed consent[b]	X	-	-	-	-	-	-
Inclusion/exclusion criteria[c]	X	X[k]	-	-	-	-	-
Medical and surgical history	X	-	-	-	-	-	-
Prior and ongoing medication	X	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-
TB screening (if required)[d]	X	-	-	-	-	-	-
Viral disease screening[e]	X	-	-	-	-	-	-
Physical examination[f]	X	X	X	X	X	X	X
Vital signs measurements[g]	X	X	X	X	X	X	X
12-lead ECG	X	-	-	-	-	X	X
Pregnancy test[h]	X	X	X	X	X	X	X
Clinical laboratory assessments[i]	X	X[l]	X	X	X	X	X
Randomization	-	X	-	-	-	-	-
Study treatment administration	-	X	X	-	-	-	-
Adverse events	X	X	X	X	X	X	X
Immunogenicity[j]	-	X	X	X	X	X	-
Blood sample for estimation of rituximab concentration	-	X	X	X	X	X	-
Concomitant medications	-	X	X	X	X	X	X

Abbreviations: ADA, anti-drug antibody; ECG, electrocardiogram; EOS, end of study; ET, early termination; EU-rituximab, European Union approved rituximab (MabThera); HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; NAb, neutralizing antibody; TB, tuberculosis; US-rituximab, United States-licensed rituximab (Rituxan).

Note: For assessments related to COVID-19, see Section 3.2 of the protocol.

[a] All subjects completing the study at Week 12 or those discontinuing the study at any time will attend an EOS/ET visit. The allowable window for the EOS/ET visit is ±7 days.

[b] Informed consent must be obtained prior to undergoing any protocol-specific procedure.

[c] All eligibility criteria must be met before a subject is randomized to study treatment. Subjects must have received at least 1 full course comprising two 1000 mg infusion of either US-rituximab at least 16 weeks or EU-rituximab at least 24 weeks prior but not more than 15 months prior to the day of randomization visit.

[d] Tuberculosis testing is to be done only if it is required by local regulations or practice.

[e] The following tests are to be conducted by each site's local laboratory: HBsAg, HBcAb, HCV, HIV, serum IgG and IgM.

Note: For HBcAb, site is requested to perform HBcAb IgG and HBcAb IgM. If any of these 2 results is positive, then the subject will be considered as screen failure.

[f] Complete physical examination will be performed at all visits. Height will be recorded at screening only.

[g] Body temperature (oral), blood pressure, heart rate, and respiration rate will be recorded at each visit. Vital signs will be monitored every 30 minutes (± 5 minutes) during the course of the treatment administration or more frequently as necessary.

[h] Subjects who are WOCBP will have a serum pregnancy test at the screening visit, Week 12 (EOS/ET), and Week 26 (additional follow-up) and a urine pregnancy test on Day 1 prior to randomization and Day 15 (before dosing), Week 4, and Week 8 visits. All tests will be performed by the local laboratory according to local practice.

[i] Clinical laboratory assessments (hematology/biochemistry/urinalysis) will be performed by the local laboratory. See Section 6.3.4 for the list of tests.

[j] Plasma samples for detection of ADA will be collected before the administration of study treatment on Day 1 and Day 15 (preferably within 30 minutes prior to infusion). Additional samples for detection of ADA will be collected at Weeks 4, 8, and 12 (EOS/ET). Samples that are confirmed positive for ADA will be further tested for titer and NAb. Details are provided in Section 6.2.

[k] Viral disease screening (HBsAg, HBcAb, HCV, and HIV), serum IgG and IgM, and TB screening will not be repeated on Day 1 of the study.

[l] Clinical laboratory assessments scheduled on Day 1 can be performed 1 day prior to dosing.

[m] Additional follow-up visit will be conducted at Week 26 to evaluate safety and to perform a serum pregnancy test in WOCBP.

14.2 Appendix 2: Classification of Functional Status in Rheumatoid Arthritis

Table 14-2: Classification of Functional Status in Rheumatoid Arthritis

Class I	Complete functional capacity with ability to carry on all usual duties without handicaps
Class II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
Class III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care
Class IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care

14.3 Appendix 3: Protocol Amendment

14.3.1 Protocol Amendment 1 – Protocol Version 2.0, Dated 12 Aug 2019

14.3.1.1 Overview of Changes

Summary of significant changes includes the following:

1. Updated exclusion criterion 2 for clarity.
2. Added Exclusion Criterion 18. Subjects with hypogammaglobulinemia (low IgG) are immunocompromised and more susceptible for both infections and side effects; hence, such subjects should be excluded.
3. 'Section 5.4.1 Packaging' has been reworded for better clarity. Further details will be captured in Pharmacy Manual/other appropriate plan. Sentence modified from:

   "Rituximab concentrate for solution for infusion will be packaged as blinded supplies in which the external packaging (carton) for all products will appear identical and identified with a unique container number."

   To

   Rituximab concentrate for solution for infusion will be packaged in a carton or kit.
4. Added following text in Section 6.1 of Schedule of Assessment in order to clarify unscheduled visit data capturing: "If any unscheduled visits happens at any time during the study, visit details/appropriate data including reason will be captured in the electronic case report forms (eCRF)."
5. Added assessment of IgG (Section 6.1.1) in-line with addition of new Exclusion Criterion 18 to exclude the subjects with low IgG.
6. Added clarification for estimation of rituximab concentration in Section 3.1.2 and Section 6.2.1, time matched blood samples for estimation of rituximab concentration were added to aid in subsequent data interpretation as and if needed. Relevant procedures (i.e. time matched blood sample collection and blood loss for estimation of rituximab concentration) are added in Section 6.1.2, Section 6.1.3, Section 6.1.4, Section 6.5, and Appendix 1.
7. Other administrative and minor formatting changes were made throughout the protocol for consistency.

14.3.1.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the study protocol are shown in bold and deletions are shown in ~~strike-through~~ text. Corrections of obvious typing errors or omissions are not highlighted.

Protocol Synopsis

- Exclusion criteria

  2. Subjects with human immunodeficiency virus **(positive HIV1Ab or HIV2Ab)**, hepatitis B virus and/or hepatitis C virus infection**, including those with positive results in the viral disease screening.**

  18. Subject with serum IgG < lower limit of normal

List of Abbreviations

LLN	**Lower limit of normal**

Pharmacodynamics (Section 1.1.1.2)

Total serum Ig levels, immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA) were decreased at 6 months with the largest change observed in IgM. At Week 24 of the first course of rituximab treatment, small proportions of patients experienced decrease in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal~~.~~ **(LLN)**. In the experience with rituximab in RA patients during repeated rituximab treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA, respectively concentrations below the ~~lower limit of normal~~ **LLN** at any time after receiving rituximab. The clinical consequences of decrease in Ig levels in RA patients treated with rituximab are unclear (Dr. Reddy's Laboratories IB).

Rationale of Study Design (Section 3.1.2)

A validated enzyme linked immunosorbent assay will be used to test ADA, titer and NAb by specialist laboratories (sponsor designated laboratories) in this study.

Along with immunogenicity sample, a time matched blood sample (approximately 5 mL) will be collected for the estimation of rituximab concentration. The evaluation of the

samples will be performed to interpret safety and/or immunogenicity data appropriately, if needed.

Exclusion criteria (Section 4.1.2):

Subjects meeting any of the following criteria must not be enrolled in the study:

2. Subjects with human immunodeficiency virus **(positive HIV1Ab or HIV2Ab)**, hepatitis B virus and/or hepatitis C virus infection**, including those with positive results in the viral disease screening (Section 6.1.1).**

18. Subject with serum IgG <LLN

Schedule of Assessments (Section 6.1)

The investigator may **plan unscheduled visits** ~~schedule visits (unplanned visits)~~ in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject. **If any unscheduled visits happen at any time during the study, visit details/appropriate data including the reason will be collected in the eCRF.**

Packaging (Section 5.4.1)

Rituximab concentrate for solution for infusion will be packaged **in a carton or kit** ~~as blinded supplies in which the external packaging (carton) for all products will appear identical and identified with a unique container number~~.

Screening Period (Day 14 to 0) (Section 6.1.1)

Screening procedures and assessments will be as follows:

The proposed chronological order of the assessments below should be followed.

14. Serum Immunoglobulin (IgG)

Treatment Period (2 Weeks) (Section 6.1.2)

Study Day 1 (Week 0, Baseline Visit)

4. Clinical laboratory assessments: a blood sample will be taken for hematology and biochemistry; urinalysis will also be performed (See Section 6.3.4 for the list of clinical laboratory assessments).

Note: Viral disease screening (HBsAg, ~~HBsAb~~ **HBcAb**, HCV, HIV), and **serum IgG and** TB screening will not be repeated on Day 1 of the study. On Day 1, clinical laboratory assessments can be performed 1 day prior to dosing.

7. **Collect a time matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.**

Study Day 15 (Week 2 + 1 Day)

5. **Collect a time matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.**

Follow-Up Period (10 Weeks) (Section 6.1.3)

Week 4 ± 7 Days

5. **Collect a time matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.**

Week 8 ± 7 Days

5. **Collect a time matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.**

End of Study/Early Termination Visit (at Week 12 ± 7 Days) (Section 6.1.4)

EOS/ET assessments are as follows:

6. **Collect a time matched blood sample (approximately 5 mL) for the estimation of rituximab concentration.**

Immunogenicity Sampling (Section 6.2.1)

Whole blood samples (approximately 10 mL) will be collected and processed to obtain approximately 4 mL of plasma for ADA (including titer and NAb) detection at each time point. Samples should be processed as per detailed instructions in the laboratory manual for collection by the central laboratory. The samples will be shipped to laboratories for ADA titer and NAb analysis by the central laboratory as detailed in the laboratory manual.

Along with the immunogenicity sample, a time matched blood sample (approximately 5 mL) will be collected for the estimation of rituximab concentration. The evaluation of the samples will be performed to interpret safety and/or immunogenicity data appropriately, if needed.

The central laboratory shipment address and assay laboratories contact information will be provided to the investigator prior to or during the initiation of the study.

Clinical Laboratory Assessments (Section 6.3.4)

Clinical laboratory assessments will be performed as indicated in Table 14-1. Hematology, biochemistry, and urinalysis will be conducted at screening, on Day 1, Day 15, and at Weeks 4, 8, and 12 (EOS/ET) visits. Serum pregnancy test will be conducted at screening and Week 12 visit. Urine pregnancy test will be conducted on Day 1 prior to randomization and **Day 15 (before dosing),** at Weeks 4 and 8 visits.

The following parameters will be assessed:

Serum IgG

Blood Loss During the Study (Section 6.5)

For the safety evaluation, approximately 10 mL of blood will be withdrawn from the subjects at each time point. A total of approximately ~~110~~ **135** mL of blood will be collected per subject during the study for immunogenicity, **for estimation of rituximab concentration** and safety evaluation as mentioned in Table 6-1.

Table 6-1 Blood Loss During the Study

Time Points	Safety Evaluation (Laboratory)	ADA and NAb Evaluation	**For estimation of rituximab concentration (Approx.)**	Total Volume of Blood Loss
Screening	10 mL	-		10 mL
Week 1/Day 1	10 mL	10 mL	**5 mL**	~~20~~ **25** mL
Week 2/Day 15	10 mL	10 mL	**5 mL**	~~20~~ **25** mL
Week 4	10 mL	10 mL	**5 mL**	~~20~~ **25** mL
Week 8	10 mL	10 mL	**5 mL**	~~20~~ **25** mL
Week 12	10 mL	10 mL	**5 mL**	~~20~~ **25** mL
Total volume of blood loss	60 mL	50 mL	**25 mL**	~~110~~ **135** mL

Abbreviations: ADA=anti-drug antibody; NAb=neutralizing antibodies

Note: For safety evaluation, more than 10 mL of blood can be withdrawn based on the site/local laboratory practice and will not be considered as deviation.

Appendix 1: Schedule of Events (Section 14.1)

Table 14-1 Schedule of Events

Study Period	**Screening Visit Days -14 to 0**	**Treatment Visit**		**Follow-Up Visits**		**EOS/ET[a] Visit**
Study Week		**0 (Day 1)**	**2 (Day 15)**	**4**	**8**	**12**
Visit Window		**+1 day**	**+1 day**	**±7 days**		
Viral disease screening[e]	X					
Pregnancy test[h]	X	X	X	X	X	X
Immunogenicity[j]		X	X	X	X	X
Blood samples for estimation of rituximab concentration		**X**	**X**	**X**	**X**	**X**
Concomitant medications		X	X	X	X	X

[e] HBsAg, HBcAb, hepatitis C virus, ~~and~~ HIV, **and Serum IgG** to be conducted by each site's local laboratory.

[h] Subjects of childbearing potential will have a serum pregnancy test at the screening visit and a urine pregnancy test on Day 1 prior to randomization **and Day 15 (before dosing),** and at Week 2, Week 4 and Week 8 visits. A serum pregnancy test will be repeated at EOS/ET visit. All tests will be performed by the local laboratory according to local practice.

[k] Viral disease screening (HBsAg, ~~HBsAb~~ **HBcAb**, HCV, and HIV), **serum IgG** and TB screening will not be repeated on Day 1 of the study.

14.3.2 Protocol Amendment 2 – Protocol Version 3.0, Dated to be added

The overall reason for this amendment is to address feedback from Paul Ehrlich Institute (PEI), Medical Regulatory Authority, Germany. Further to these changes, minor revisions for clarity, formatting, abbreviations, and spelling changes have been made throughout the document.

14.3.2.1 Overview of Changes

Summary of significant changes includes the following:

- The duration of study is extended by 6 months post treatment. The study now includes an additional follow-up visit at Week 26 (24 weeks [6 months] after the last study treatment administration on Day 15). At the additional follow-up visit (Week 26), safety will be evaluated and a serum pregnancy test will be performed in WOCBP. Further it is also clarified in the protocol that subjects need to re-consent if they want to continue participating in the study after Week 12 through Week 26. Additional text/clarity has been included when a subject requires rescue therapy/re-dosing of rituximab after Week 12.
- New text has been added and existing text has been revised as applicable throughout the protocol, with the following affected sections: Protocol Synopsis (Study Design and Estimated Study Duration sections), Section 3.1.1 (Description), Section 3.1.2 (Rationale of Study Design), Section 3.1.4 (End of Study), Section 4.2 (Withdrawal of Subjects From Study Treatment and/or Study), Section 4.2.2 (Handling of Withdrawals), Section 5.7 (Blinding), Section 6.1.5 (Additional Follow-up Visit [Week 26]), Section 6.3.1.2 (Recording of Adverse Events), Section 6.3.4 (Clinical Laboratory Assessments), Section 6.5 (Blood Loss During the Study), Section 11.4 (Final Report), and Appendix 1 (Schedule of Events).

Reason: Above changes have been done to address recommendations from PEI, Medical Regulatory Authority, Germany to follow subjects for safety in line with SmPC and for further monitoring of contraception in WOCBP until 6 months post-dose considering the longer half-life of Rituximab (approximately 20 days).

- Clarified that the final CSR will be prepared after the EOS (Week 12) is achieved by all subjects. Data for the time period from Week 12 through Week 26 (additional follow-up) will be presented as an addendum to the final CSR.

- Text regarding this clarification revised in the following sections: Section 3.1.1 (Description), Section 5.7 (Blinding), and Section 11.4 (Final Report).

Reason: Changes have been made in accordance with the changes of extending the study up to 26 weeks (as mentioned above) as all the data required for the primary objective would have been collected by Week 12.

- Detailed information regarding study conduct and contingency measures to be taken for smooth functioning of the study during the COVID-19 pandemic are added. In addition, benefit-risk assessment of rituximab treatment during the COVID-19 pandemic have also been discussed in the protocol.
- New section (Section 3.2 [Study Conduct During the COVID-19 Pandemic]), including subsections (Section 3.2.1 [Benefit-Risk Assessment of Rituximab Treatment During the COVID-19 Pandemic] and Section 3.2.2 [Contingency Measures Taken During the COVID-19 Pandemic]) are added.

Reason: Above changes have been made to describe the risk-benefit assessment of the study conduct along with risk mitigation measures and to describe contingency measures for the ongoing COVID 19 pandemic, as also recommended by PEI, Medical Regulatory Authority, Germany.

- Exclusion Criterion #6 has been revised in Protocol Synopsis and Section 4.1.2 (Exclusion Criteria) to update the requirement of historical "severe" hypersensitivity to US-rituximab or EU-rituximab or any of its excipients requiring drug discontinuation to any severity of hypersensitivity to these treatments or excipients.

Reason: Above change has been made to avoid the risk of hypersensitivity reaction in the subject as an additional safety measure.

- Exclusion Criterion #16 updated to include definition of WOCBP and highly effective birth control measures per the CTFG 2014 guidelines in Protocol Synopsis and Section 4.1.2 (Exclusion Criteria).

Reason: Above change has been made to define WOCBP and to describe highly effective measures of birth control as per the CTFG 2014 guidelines. This change is also considered for better clarity and in line with the recommendation from PEI, Medical Regulatory Authority, Germany.

- Exclusion Criterion #17 related to subjects who are men involved in any sexual intercourse that could lead to pregnancy is updated in Protocol Synopsis and Section 4.1.2 (Exclusion Criteria) to clarify that sexually active male subjects (unless permanently sterile by bilateral orchidectomy), who do not agree to use 1 of the highly effective methods of birth control during treatment and for at least 12 months after the last administration of study treatment, will be excluded from the study.

Reason: Above change has been made to describe highly effective measures of birth control as per the CTFG, 2014 guidelines and for better clarity and in line with the recommendation from PEI, Medical Regulatory Authority, Germany.

- Clarified that if a subject withdraws consent for further study treatment, but not for study participation, the subject can continue further visits and data can continue to be collected until Week 26. However, if a subject withdraws consent for further participation in the study there will be no further data collection and the subject will be discontinued from the study. Subjects need to re-consent to continue participating in the study after Week 12 through Week 26, If a subject does not re-consent, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.
  - Text added for this clarification in Protocol Synopsis (Study Design), Section 3.1.1 (Description), Section 4.2 (Withdrawal of Subjects From Study Treatment and/or the Study), Section 4.2.1 (Reasons for Withdrawal/Discontinuation), and Section 4.2.2 (Handling of Withdrawals)

Reason: Above change has been made to categorize withdrawal criteria (i.e. consent withdrawal for further study treatment or for further study participation) and to make it uniform with the section 4.2.2 (Handling of Withdrawals).

- Text in Section 4.2.2 (Handling of Withdrawals) revised to emphasize that subjects can take their own independent decision to withdraw from study treatment and/or study participation at any time.

Reason: Above change has been made to emphasize that subjects can take their own independent decision to withdraw from study treatment and/or study participation. Moreover, text has been revised to add the clause for the consent withdrawal at Week 12 based on the earlier change of extending study duration up to Week 26, post-dose.

- Clarified that MTX and folic acid, which are background medications in the study, should be used in accordance with the guidelines specified in the local labels. Also, clarification has been provided that folinic acid at the same dose of folic acid, can be given in place of folic acid if it is allowed by the local label. A note has been added in protocol synopsis (Study Treatment, Dosage, and Route of Administration) and Section 5.9.1 (Background Medications).

Reason: Above change has been made in line with the recommendation from PEI, Medical Regulatory Authority, Germany and for better clarity to the investigators

- Complete physical examination will be performed now at all study visits and not as indicated only at screening and EOS/ET visits in the Schedule of Assessments of the earlier protocol (Version 2.0, Amendment 1).

o Text updated in the following sections: Section 6.1 (Schedule of Assessments [including relevant subsections]) and Appendix 1 (Schedule of Events; footnote "f").

Reason: Above change has been made for better clarity and for uniformity across the document.

- Information regarding immunological testing in humans has been included in Section 6.2.2 (Immunogenicity Assay).

Reason: Above change has been made to add more information about the testing/methods of primary endpoints.

- Detailed definitions of IRRs and hypersensitivity reactions is added in Section 6.3 (Safety Assessments).

Reason: Above change has been made to guide the investigator while differentiating IRRs, hypersensitivity reactions and/or anaphylaxis.

- Clarified that all ongoing SAEs should be followed up until resolution or stabilization or until a pre-defined outcome is reached, whereas all ongoing nonserious AEs should be followed up until resolution or stabilization or the EOS/ET visit, whichever occurs first, except any ongoing treatment-related nonserious AEs that should be followed until that AE is stabilized, resolved, or, in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying condition.

o Text updated and note has been added in Section 6.3.1.2 (Reporting of Adverse Events).

Reason: Above changes have been made for better clarity and in line with the recommendation from PEI, Medical Regulatory Authority, Germany.

- Clarification note has been provided for assessment of adverse events outcome in Section 6.3.1.4 (Assessment of Causality).

  Reason: Above change has been made for better clarity to the investigator.

- Absolute neutrophil count is added to the list of hematology parameters to be assessed in the study. List of hematology parameters to be assessed in the study are provided in Section 6.3.4 (Clinical Laboratory Assessments) updated.

Reason: Above change has been made to clarify and to emphasize safety evaluation i.e. late neutropenia and also in line with earlier changes.

- Serum FSH testing will be performed in postmenopausal women.
  - Text added in Section 6.3.4 (Clinical Laboratory Assessments).

Reason: Above change has been made in line with earlier changes and per the CTFG guidelines 2014.

- Clarification note is added for HBcAb evaluation
  - A clarification note is added in the Section 6.1.1 (Screening Period [Days -14 to 0]), Section 6.1.2 (Treatment Period [(2 Weeks]), Section 6.3.8 (Viral Disease Screening) and in Appendix 1 (Schedule of Events; footnote "e").

Reasons: Above changes have been done for better clarity to the investigators.

- Additional Serum Immunoglobulin evaluation (IgM) is added in the Section 6.1.1 (Screening Period [Days -14 to 0]), Section 6.1.2 (Treatment Period [2 weeks]; Study Day 1 [Week 0, Baseline visit]), Section 6.3.4 (Clinical Laboratory Assessments), and in Appendix 1 (Schedule of Events; footnote "e" and footnote "k")

Reasons: Above change has been made in line with the recommendation from PEI, Medical Regulatory Authority, Germany

- All references to legally authorised or legally acceptable representatives or subject's legal guardian and any equivalents have been removed. Moreover, it is further clarified that the

study sites are advised to follow local or country-specific guidelines while obtaining consent from the subject.

- Text added in Section 9.1 (Independent Ethics Committee or Institutional Review Board), Section 9.3 (Subject Information and Consent). Section 10.1 (Confidentiality).

Reason: Above change has been made to remove all references of legally authorised or legally acceptable representatives or subject's legal guardian and any equivalents from the protocol with consideration that only those subjects who are capable of providing informed consent will be included in this clinical study. This change has also been done in line with the recommendation from PEI, Medical Regulatory Authority, Germany.

- The sponsor contact details on the title page of this protocol are updated.

Reasons: Administrative change

Minor revisions for clarity, formatting, abbreviations, and spelling changes have been made throughout the document.

Protocol Clarification Letter #1

22 Jul 2020

To Whom So Ever It May Concern

This letter is to inform you about an typographical error in clinical study protocol of RI-01-007 titled "**A Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Immunogenicity and Safety of Transitioning Subjects With Rheumatoid Arthritis to Biosimilar Rituximab (DRL_RI) or Continued Treatment With Rituxan® or MabThera®**" Version 3.0 Amendment 2, dated 10 Jul 2020. The following sections require further clarification:

"Protocol Amendment 2 – Protocol Version 3.0, Dated to be added" is mentioned in Table of contents (Section 14.3.2) and in the title of Section 14.3.2 which should be read as "Protocol Amendment 2 – Protocol Version 3.0, Dated 10 Jul 2020".

This letter will serve as documentation of this typographical change to protocol RI-01-007. If at a later date the protocol is amended, this change will be incorporated into the document at that time.

Sincerely,

CI [redacted]

Dr.Reddy's

CI [redacted]

Study: RI-01-007

Objective: Clarification Letter

Dear Investigators,

We have started the enrolment of patients for the Study RI-01-007 and during the Eligibility package review process, we have observed the issues for following the Exclusion criterion n° 2:

> *Subjects with human immunodeficiency virus (positive HIV1Ab or HIV2Ab), hepatitis B virus and/or hepatitis C virus infection, including those with positive results in the viral disease screening (Section 6.1.1).*

To verify EC 2 is not met, some sites are only testing IgM-HBc antibodies. Due to the risk of HBV reactivation with rituximab patients with HBV infection, recent or past, are not eligible for the study. Therefore, to verify EC 2 is not met, in addition to negative HBsAg, both IgM-HBc and IgG-HBc antibodies tests are required.

We are clarifying that for the HBV Viral disease screening, local laboratory needs to perform HBsAg anti-HBc antibodies (both IgM and IgG). If any of these 3 results is positive, then the subject will be considered as screen failure.

This clarification has been included in the incoming Protocol Amendment, but in the meantime until it will be approved at your site in order to preserve the patient safety (recent and chronic Hepatitis B is excluded) we would like to clarify on the need for IgG-HBc antibodies testing to avoid additional patient sample collection or patient declared screening failure for not having complete Hepatitis B assessment.

CI [redacted]

CI [redacted]