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: 16 Mar 2022

Dr. Reddy's Laboratories S.A.

RI-01-007

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®

16MAR2022

Statistical Analysis Plan

Version *2.0*

CI [redacted]

CI [redacted]

TABLE OF CONTENTS

List of Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CRF	Case report form
CTCAE	Common terminology criteria for adverse event
ECG	Electrocardiogram
EOS	End of study
EOSI	Event of Special Interest
ET	Early termination
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRR	Infusion-Related Reactions
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibodies
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SAS	Statistical analysis system
TB	Tuberculosis
TEAE	Treatment-emergent adverse events
TNF	Tumor necrosis factor
TMRC	Time matched rituximab concentration
US	United States
WHO	World Health Organization
WOCB	Women of childbearing potential

1. Introduction

This document describes the rules and conventions to be used in the presentation and analysis of immunogenicity and safety of clinical study RI-01-007. This is 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®"*.

This statistical analysis plan (SAP) is based on protocol version 3.0, Amendment 2 dated 10 Jul 2020 and eCRF version 3.0, dated 18 Dec 2020. The SAP is prepared in compliance with International Council on Harmonisation (ICH) E9 and Addendum on Estimands and Sensitivity Analysis in Clinical Trials E9 R1 will be finalized and approved before the database is locked. Any deviation from the final SAP after database lock will lead to an SAP addendum and will be described in detail in the clinical study report (CSR), along with reasons for the change.

DRL_RI (Dr. Reddy's Rituximab) has been developed by Dr. Reddy's Laboratories S.A and is intended to be developed as a biosimilar version of the chimeric anti-CD20 monoclonal antibody, rituximab.

Rituximab is licensed in the United States as Rituxan® (Reference product, RP) and approved in the European Union as MabThera® (Reference medical product, RMP) for use in B-cell non-Hodgkin's Lymphoma (NHL), chronic lymphocytic leukemia, rheumatoid arthritis (RA) in combination with methotrexate (MTX) in adult subjects with moderately to severely active RA who had an inadequate response to one 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 will be referred to as US-rituximab; MabThera® will be referred to as EU-rituximab; DRL_RI is being developed as a biosimilar of Rituximab and will be referred to as DRL_RI in this study.

DRL_RI is a chimeric human/murine IgG1 kappa monoclonal antibody consisting of murine light and heavy chain variable regions and human constant region sequences. The primary amino acid sequence is identical and the secondary and tertiary structures of DRL_RI are indistinguishable from the RMP and RP 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 investigator brochure for DRL_RI (Dr. Reddy's Laboratories IB).
In the DRL_RI development program, Study-RI-01-003 was a Phase I/II, randomized, double-blind study comparing the PK and PD of DRL_RI with RMP and RP 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 objective of the current study (RI-01-007) is to assess the immunogenicity and safety of transitioning subjects with RA to DRL_RI from RMP or RP to continued treatment with US-rituximab/EU-rituximab.

2. Study Objectives

The objectives of the study are included below:

- 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.

3. Investigational Plan

3.1. Overall Study Design and Plan

This study is a phase 3, randomized, double-blind, parallel group, multicentre study to assess the immunogenicity and safety of two 1000 mg IV infusions of DRL_RI or continued treatment with Rituxan® or MabThera® in approximately 140 subjects (70 per treatment arm) in transitioning to biosimilar Rituximab (DRL_RI) or continued treatment with Rituxan® or MabThera®.

Baseline is defined as the last available value prior to the first dose of study drug administration. For Vital Sign timepoint assessment are scheduled on Day 1 and Day 15, if the time is missing then Day 1 Pre-dose will be considered as baseline.
The study will include screening period (Days -14 to 0) and a double-blind period (Day 1 to Week 12), which consist 2 weeks of treatment period and 10 weeks of follow-up period for safety and immunogenicity. 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).

Re-screening will be allowed for those subjects who do not meet the criteria for participation in this study (screen failure) at the investigator's discretion, following discussion with the sponsor designee medical monitor.

Eligible subjects will be randomized in permuted blocks in 1:1 ratio 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. Randomization schedule will be stratified by region (US/EU).

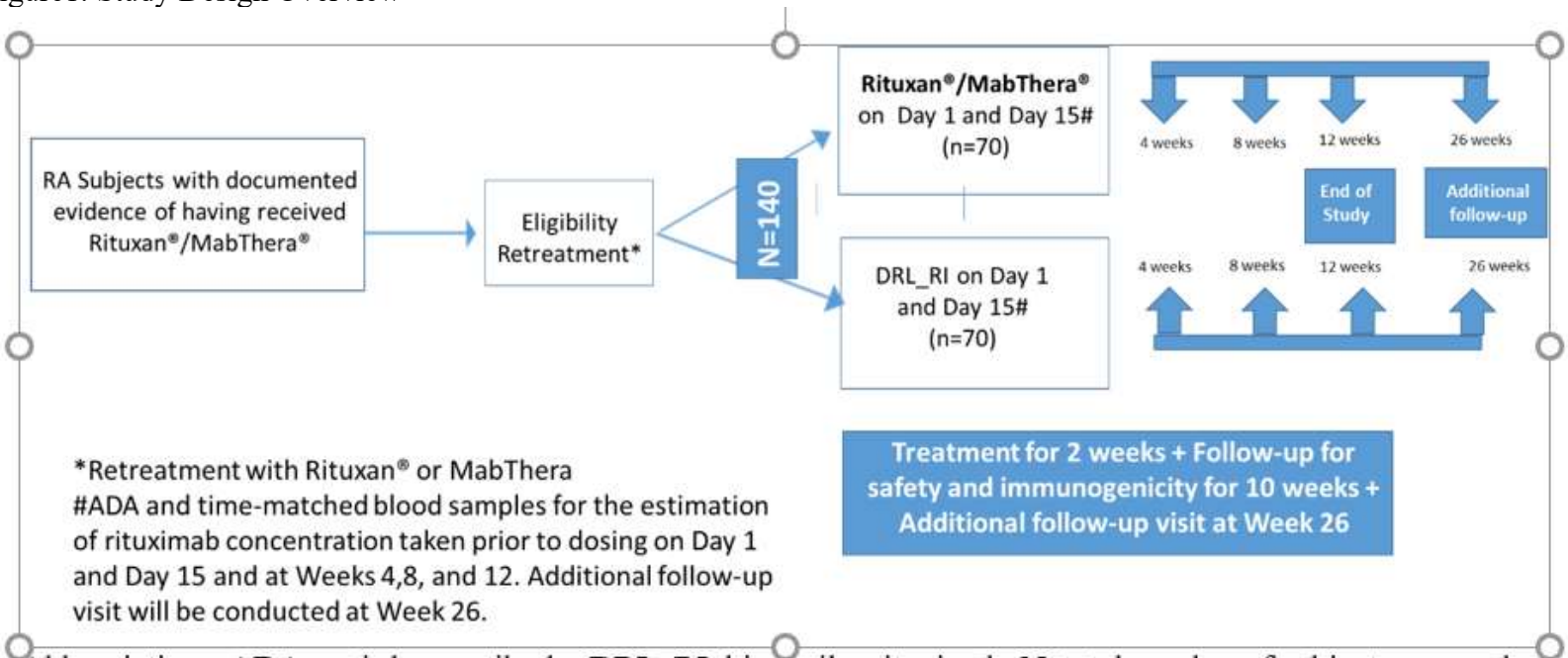
Subjects having signed the informed consent form (ICF) versions prior to the protocol version 3.0, Amendment 2 need to re-consent to continue participating in the study after Week 12 through Week 26. If a subject does not re-consent for further study participation after Week 12, then his/her study data up to Week 12 will be collected and the subject will be discontinued from the study.

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 before Week 12 will attend an EOS/early termination (ET) visit. Furthermore, subjects completing the follow-up at Week 26 or discontinued after Week 12 will attend Week 26/early termination (ET) visit.

The study endpoints are the incidence of ADA (Anti-drug antibody), including titer and Nab (Neutralizing antibodies) primary safety endpoints of TEAEs (Treatment-emergent adverse events), SAEs (Serious adverse event), anaphylactic reactions, hypersensitivity reactions, infusion-related reactions (IRRs); and other safety endpoints of clinical laboratory parameters, vital signs, twelve-lead electrocardiogram (ECG) and physical examination. 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. 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 Schedule of Events is presented in Appendix 12.1 and the study design overview is illustrated in Figure 1 below.

Figure1: Study Design Overview



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.

3.2.Study Endpoints

The study endpoints are as below.

The immunogenicity endpoint is:

- The incidence of anti-drug antibodies (ADA), including titer and neutralizing antibodies (NAb).

The immunogenicity endpoint is measured while on study over up to 12 weeks or until death, regardless of use of prohibited therapies or treatment missed/discontinuation due to any other reasons.

The primary safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
- Incidence of anaphylactic reactions, hypersensitivity reactions, and Infusion-related reactions (IRRs).

Other safety endpoints are:

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

The safety endpoints are measured while on study or until death, regardless of use of prohibited therapies or treatment missed/discontinuation due to any other reasons.

Exploratory endpoints are:

The exploratory endpoints, and descriptions of estimands are presented in Table 1. Details of attributes, intercurrent events, and handling strategies of the estimands are presented in Table 2.

Table 1: Endpoints, and Estimands

Endpoints	Exploratory Estimands
Immunogenicity Endpoint: • Development of Anti-drug antibodies (ADA), including titer and neutralizing antibodies (NAb)	**Estimand 1 (Immunogenicity)** Immunogenicity will be evaluated using incidence of positive ADA including Nab in subjects with active RA who are who are currently in treatment with US-rituximab or EU-rituximab and are eligible for the subsequent treatment course with US-rituximab or EU-rituximab. The development of ADA is measured while on study over up to 12 weeks or until death or use of prohibited therapies with impacts on immunogenicity assessments whichever is earliest, regardless of treatment missed/discontinuation due to any other reasons or COVID-19/SARS-CoV-2 infection.
Primary Safety Endpoints: • Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Anaphylactic reactions, hypersensitivity reactions, and Infusion-related reactions (IRRs)	**Estimand 2 (Safety - AEs)** Counts and percentages of eligible subjects who are treated and would develop TEAES or SAEs

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation [SD], median, quartiles, minimum, and maximum). Categorical data will be described using the count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of subjects within the analysis population of interest, unless otherwise specified. Percentages will be presented to one decimal place.

For Time Matched Rituximab Concentrations (TMRC) sample, concentration below the lower limit of quantification (BLLOQ) will be converted to '0' for the purpose of quantitative summaries, but will be presented as recorded, i.e. BLLOQ in listings.

Data will be displayed in all listings sorted by subject number and visit, if applicable. Listings will include all visits including unscheduled visits.
"No data available for this report" will be presented when there are no data available to report.
Unless otherwise specified, baseline will be defined as the last non-missing value collected before the first study drug administration. Study day is defined as:

- Visit/examination date – date of first study drug administration when date is prior to the date of first study drug administration (day 1).
- Visit/examination date – date of first study drug administration + 1 when date is on or after day 1.

For summaries by visit, if multiple records fall on the same visit and timepoint, then the record which is the earliest value will be chosen.

Unscheduled results will not be summarized but will be listed, unless otherwise specified. Post baseline summaries will include all values collected after the date of first study drug administration.

All efforts will be made to ensure that all values are populated for start date, stop date, severity and causality of AE. In case of any missing or partial dates, for the purpose of inclusion in tables, incomplete AE stop dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively) will be imputed as follows:

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If subject dies during the study, the stop date will be imputed as the date of death if the imputed stop date is after date of death.
All analyses of the data will be conducted using SAS® software version 9.4 or higher.

Unless specified otherwise, summaries of safety and TMRC will be based on safety population and immunogenicity data will be based on the immunogenicity population.

4.1. Sample Size

CI

4.2. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used to administer the randomization schedule. CI Biostatistics department has generated the randomization schedule using SAS® software version 9.4 for IWRS, which links sequential subject randomization numbers to treatment codes. The randomization schedule is stratified by region (US/EU). It has also used an appropriate block size, which will not be revealed until the database lock.

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

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 study report will include all data including all end points after all subjects have completed Week 12 (EOS/ET) visit and subsequent additional follow-up data from Week 12 to 26.

Emergency unblinding can 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. In such situation 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.

Subjects who withdraw or discontinue before or after the randomization their subject identification number will not be re-used.

4.3. Analysis populations

The analysis populations that will be used in this study are:

- Safety population
- Immunogenicity population

4.3.1. Safety population

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

4.3.2. Immunogenicity population

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

4.3.3. TMRC population

TMRC population will include all subjects who have received at least one dose of study drug and have a valid TMRC concentration available.

5. Subject Disposition

5.1. Disposition

A summary of screen failures will be provided including the number and percentage of subjects for the following categories: subjects screened, subjects who failed screening and the primary reason for screen failure ("Inclusion/Exclusion criteria not met" "IN01" to "EX18" and "Withdrew consent").
A listing of screen failures will be presented.

A summary of the analysis populations includes the number and percentage of subjects in safety and immunogenicity populations. This summary will also include the number and percentage of subjects for the following categories:

- Subjects in the safety population.
- Subjects excluded from safety population along with reasons.
- Subjects in the immunogenicity population
- Subjects excluded from the immunogenicity population along with reasons.
- Summary of disposition will include:
    - Subjects who completed week 12 visit.
    - Subject who completed study treatment.
    - Subject who discontinued study treatment along with reasons.
    - Subjects who terminated study prior to week 12 along with reasons.
    - Subjects who did or didn't reconsent for week 26.
    - Subject completed study (week 12) with protocol version 2.
    - Subjects who completed week 26 visit.
    - Subjects who discontinued prior to week 26 visit along with reasons.

Summary will be provided for all randomized subjects and all percentages will be based on the number of subjects randomized.

Subject disposition data will be presented in a listing for all randomized subjects.

5.2. Study Deviations

A study deviation is any change, divergence, or departure from the study design or procedures defined in the Protocol or to ICH GCP E6(R2), or non-compliance with applicable regulatory requirements.

A significant study deviation is one that may affect the interpretation of study results or the subject's rights, safety or welfare. Whereas, a non-significant protocol deviation is one that does not impact the objective, primary and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the study.

Total number of events (e), and number of subjects with protocol deviations and ICH/GCP deviations by categories (significant and non-significant) will be summarized for the safety population and occurrence of COVID-19 or related events will be summarized separately.

Study deviation data will be presented in a listing for the safety population. Occurrence of COVID-19 or related events will be listed separately. The site level ICH/GCP deviations will not be included in summary and subject listings.

5.3. Covid-19 Test

If a subject has an event suspected to be Coronavirus Disease - 2019 (COVID-19) or related event, the investigator will perform COVID-19 test per local health authority or study site guidance at scheduled visits.

Covid-19 testing data will be presented in a listing.

5.4. Missed Visit or Assessment Due to COVID-19 or related events

Missed Visit or Assessment due to COVID-19 or related events will include the number and percentage of subject for following categories.

- Missed visit/assessment due to COVID-19 or related events along with reasons.
- Missed visit due to COVID-19 or related events

The summary and listing data will be presented in a listing for safety population and COVID-19 or related event Study Disruptions listing will be listed separately.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consists of age (years), gender, race, ethnicity. The baseline characteristics consists of baseline height (cm), baseline weight (kg), baseline body mass index (BMI) (kg/m^2), country, region and fertility status (for female subjects only). Body mass index will be calculated as (body weight in kilograms) / (height in meters)^2.
Age (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of subjects by gender (Male, Female), race (Asian, White, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Black or African American, Other), ethnicity (Hispanic or Latino, Not Hispanic or Not Latino and Unknown), country (Bulgaria, Czech Republic/Czechia, Germany, Hungary, Lithuania, Poland, United States), region (EU, US) and Fertility status as per protocol version 2 and version 3 (Potentially able to bear Children, Post-Menopausal, surgically sterilized, Other) will be reported. For all, percentages will be based on the total number of subjects in the safety population.

Subject demographic and baseline characteristics will be presented in a listing.

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized and listed for the safety population:

- Origin of Rituximab drug
- Duration of rheumatoid arthritis (Days) at Randomization.
- Duration of rheumatoid arthritis (Days) = (date of randomization - date of first diagnosis).
- Duration of last rheumatoid arthritis treatment (Days) = (date of randomization - date of last RA treatment date).
- Number of treatment course(s) with rituximab.

6.3. Viral Serology

Viral serology tests will be performed for determination of the subject's eligibility. The following tests will be summarized and listed for the safety population:

- Hepatitis B Test: HbsAg (hepatitis B surface antigen), and HbcAb (hepatitis B core antibody). Results will be classified as "Negative", "Positive" or "Not done".
- Hepatitis C Test: HCV Ab (hepatitis C virus antibody). Result will be classified as "Negative", "Positive" or "Not done".
- Human immunodeficiency virus (HIV) Test: HIV – 1 Ab/HIV – 2 Ab. Result will be classified as "Negative or non-reactive", "Positive or reactive" or "Indeterminate".

6.4. Serum IgG (Immunoglobulin G) and IgM (Immunoglobulin M)

Serum IgG (immunoglobulin G) and Serum IgM (immunoglobulin M) test will be performed at screening visit for determination of the subject's eligibility.

Subject serum IgG and IgM result and specific details will be presented in a listing.

6.5. Tuberculosis Assessment

Tuberculosis (TB) assessment will be performed at screening visit only if it is required by local regulations or practice.

Subject TB assessment data including specific details will be presented in a listing.

6.6. Medical History

6.6.1. General Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher available later version. The number and percentage of subjects with any medical and/or surgical history will be summarized overall and for each system organ class. Percentages will be calculated based on number of subjects in the safety population.

Subject's medical and surgical history data including specific details will be presented in a listing.

6.6.2. Rheumatic Disease History

Rheumatic disease history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher available later version. The number and percentage of subjects with any Rheumatic disease history will be summarized overall and for each system organ class. Percentages will be calculated based on number of subjects in the safety population.

Rheumatic disease history will be listed by condition/surgery with start and stop date.

6.7. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in sections 4.1.1 and 4.1.2 of the protocol. List of inclusion criteria not met, and exclusion criteria met will be listed for all enrolled subjects.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

A prior medication is defined as any medication that is taken within a month prior to screening visit and stop date prior to the first dose of study drug. A concomitant medication is defined as any medication taken at randomization and which continue to be taken during the study and medications started during the study that has a stop date on or after the date of first dose of study drug.

If the stop date is partially/completely missing, then the question on the eCRF; "If stop date is unknown, was this drug stopped before the first administration of study drug?" will be used for classification of the medication. If the answer is "Yes" then the medication will be classed as prior medication and if the answer is "No" then the medication will be classed as concomitant medication.

If the stop date is completely missing and medication is 'ongoing' then the medication will be classed as concomitant medication.

The total number of prior and/or concomitant medications and the number and percentages of subjects with at least one prior and/or concomitant medication will be summarized by treatment arm and listed by drug class (Anatomical Therapeutic Chemical (ATC) level 4) and preferred term. All summaries will be performed using the safety population.

A rescue medication is defined as medications with the indication rheumatoid arthritis started after the administration of the first dose of study drug unless allowed by Protocol at any time during the study and until the additional safety follow-up visit at Week 26. Rituximab given as a re-dosing as per the applicable Prescribing Information/SmPC at the time of patient treatment should not be considered as rescue medication. The total number of rescue medications and the number and percentages of subjects with at least one rescue medication will be summarized by treatment arm and listed by drug class (Anatomical Therapeutic Chemical (ATC) level 4) and preferred term. All summaries will be performed using the safety population.

7.2. Study Treatments

The study treatments (DRL_RI or US-rituximab/EU-rituximab) solution for infusion will be prepared by unblinded pharmacist designated as site team member in this study and will be administered two 1000 mg IV infusions separated by 2 weeks on Day 1 and Day 15. Subject will be pre-medicated with an antipyretic and an antihistamine 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.

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 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. 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.

7.2.1. Treatment Compliance and Modifications

The number and percentage of subject with dose administered will be summarized on Day 1 and Day 15. The number and percentage of subjects with dose interruption with reason for interruption will be presented by visit. In addition, descriptive statistics for the total dose administered, and percentage of dose administered will be summarized by treatment arm. Summaries will be based on the safety population.

Percentage of dose received will be estimated based on the proportion of total dose administrated.

Dose received (%) = 100 * (total dose administered / total plan dose).

A listing will be provided for the safety population showing the details of study drug administration and pre-medication.

8. Immunogenicity Analysis

8.1. Analysis of Immunogenicity Endpoints

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

Summary statistics (frequency and percentage) by treatment arm and overall will be provided for the percent of subject with ADA formation at Day 1 and Day 15, and at weeks 4, 8, 12 (EOS/ET) visit. A subject is considered as ADA positive during the study if the subjects had at least one ADA positive sample otherwise the subject is regarded as ADA negative. Note this will also include any unscheduled visits during the study period.

Additionally, for subjects who are ADA positive at baseline, a shift table per treatment arm will be generated. The shift table includes numbers in each class (decreased, stable, and increased) as well as percentages relative to the number of ADA positive subjects with an available evaluation at the specific visit.

Subjects will be classified at each visit post baseline as:

- Decreased: If ADA titer at post-baseline visit decreases to a lower titer than that observed at baseline. Subjects with positive ADA at baseline in whom a titer is not detectable or non-evaluable at a corresponding post-baseline visit is decreased if the ADA turn negative.
- Stable: If ADA titer equal to that at baseline.
- Increased: If ADA titer increasing to a higher titer than that observed at baseline. Subjects with Negative ADA at baseline in whom a titer is not detectable or non-evaluable at a corresponding post-baseline visit is increased if the ADA turn positive.

The titer and the concentration of confirmed positive results will be reported. In addition, confirmed positive ADA samples will be analyzed for their neutralization potential in a neutralizing antibody (NAb) assay.
The incidence of ADA positive subjects and subjects with NAb will be summarized by treatment arms, by visit and overall. Antibody titers will be summarized by median and quartiles by treatment arm and visit.

A listing of immunogenicity data (including titer, concentration, ADA and Nab status) will be provided.

8.2. Time Matched Rituximab Concentration (TMRC) Analysis

A time matched blood sample (approximately 5 mL) will be collected before administration of study drug on Day 1 and Day 15, and at Weeks 4, 8, 12 (EOS/ET) visit for the estimation of concentration of rituximab

A listing of time matched rituximab concentrations (TMRC) will be provided. Also, summary statistics by treatment arm and visit will be provided by mean, standard deviation (SD), minimum (min), maximum (max), median and quartiles.

8.3. Analysis of Exploratory Endpoints

Possible intercurrent events (IcEvs) in this study are presented in Table 2.

Table 2: Intercurrent events

Label	Intercurrent Event
IcEv1 (Death)	Death due to any cause
IcEv2 (Prohibited therapy)	Use of prohibited therapy that interferes with the evaluation of immunogenicity
IcEv3 (Missed/Discontinuation of IMP)	Missed/Discontinuation of IMP without receiving the second infusion as scheduled at Day 15 due to any reasons
IcEv4 (COVID-19/SARS-CoV-2 infection)	Incidence of COVID-19/SARS-CoV-2 infection after infusion.

Attributes for the immunogenicity and safety estimands with strategies for handling IcEvs are presented in Table 3. Safety estimands are presented here together with the immunogenicity estimands for ease of reference to estimands.

Table 3: Immunogenicity and Safety Estimand

Estimand Label	**Estimand 1 (Immunogenicity)**
Estimand Description	Immunogenicity will be evaluated using incidence of positive ADA including Nab in subjects with active RA who are currently in treatment with US-rituximab or EU-rituximab and are eligible for the subsequent treatment course with US-rituximab or EU-rituximab. The development of ADA is measured while on study over up to 12 weeks or until death or use of prohibited therapies with impacts on immunogenicity assessments whichever is earliest, regardless of treatment discontinuation due to any other reasons.
Target Population	Subjects with active RA who are eligible for the subsequent treatment course with US-rituximab or EU-rituximab and would meet other study entry criteria and receive at least 1 dose of study treatment
Endpoint	Development of ADA, including titer and NAb
Treatment Conditions	Test: two 1000 mg infusions of DRL_RI Reference: two 1000 mg infusions of US-rituximab/EU-rituximab
Population-Level Summary	Incidence of ADA, including titer and NAb
Intercurrent Event (IcEv) Strategy	
IcEv1 (Death)	While-on-treatment strategy (measurements of the endpoint up until the time of the intercurrent event)
IcEv2 (Prohibited therapy)	While-on-treatment strategy
IcEv3 (Missed/Discontinuation of IMP)	Treatment policy strategy
IcEv4 (COVID-19/SARS-CoV-2 infection)	Treatment policy strategy
Rationale for Strategies	The immunogenicity assessment is to evaluate the incidence of ADA over a period whilst on study over up to 12 weeks and prior to the occurrence of intercurrent events without use of prohibited therapies. Hence, while on treatment policy is used to utilize the data until death or data prior to the prohibited medication. A treatment policy strategy is used for assessing immunogenicity irrespective of missed/discontinuation of IMP and COVID-19/SARS-CoV-2 infection.

Estimand Label	**Estimand 2 (Safety - AEs)**
Estimand Description	Counts and percentages of eligible subjects who are treated and would develop TEAES or SAEs A treatment policy strategy is used for assessing safety irrespective of any intercurrent events. Death is included as part of the endpoint (composite strategy).
Target Population	Subjects with active RA who are eligible for the subsequent treatment course with US-rituximab or EU-rituximab and would meet other study entry criteria and receive at least 1 dose of study treatment
Endpoint	Occurrence of TEAEs, SAEs, and AEs leading to withdrawal
Treatment Conditions	Test: two 1000 mg infusions of DRL_RI Reference: two 1000 mg infusions of US-rituximab/EU-rituximab
Population-Level Summary	Percentage of subjects who develop each type of AEs
Intercurrent Event (IcEv) Strategy	
IcEv1 (Death)	Composite strategy
IcEv2 (Prohibited therapy)	Treatment policy strategy
IcEv3 (Missed/Discontinuation of IMP)	Treatment policy strategy
IcEv4 (COVID-19/SARS-CoV-2 infection)	Treatment policy strategy
Rationale for Strategies	Deaths would be analyzed as part of the safety endpoint as per normal practice. A treatment policy strategy is used for assessing safety irrespective of any other intercurrent events.

9. Safety Analysis

Safety estimands are defined in Table 3. Since, all the intercurrent events follows treatment policy there will be no change in the counts summarized. Hence, single table will be generated as per safety endpoints and none for Estimand 2. All safety analysis will be performed on the safety population unless otherwise specified.

9.1. Adverse Events

An adverse event (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.
A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- Begins on or after the first dose of study drug.
- Begins before the first dose of study drug and worsens in severity on or after the first dose of study drug.

A SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or important medical event.

All adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0 or higher or available latest version). The severity of the AE will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or available latest version. AEs that are missing a severity will be imputed as 'Severe' but will be presented in the listing with a missing severity.

All TEAEs and AE for rescue medication will be summarized and presented in a listing for the safety population.

9.1.1. Incidence of Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment arm. Adverse events will be presented by SOC and PT. For subject's counts, subjects who report more than one

event will be only be counted once for each level of SOC and PT. Percentages will be based on the number of subjects in the safety population.

An overview summary of the total number of events (e), and the number of subjects and percentage of subject with any of the following will be presented.

i)	TEAE,
ii)	Serious TEAE.
iii)	Drug-Related TEAE,
iv)	Drug-Related Serious TEAE,
v)	TEAE leading to treatment discontinuation,
vi)	Serious TEAE leading to treatment discontinuation,
vii)	TEAE leading to Death
viii)	Drug-Related TEAE leading to Death
ix)	TEAE of grade 3 or higher
x)	TEAE Classified as Hypersensitivity Reactions,
xi)	TEAE Classified as Infusion Related Reactions,
xii)	TEAE Classified as Anaphylactic Reactions,
xiii)	TEAE Classified as Hypersensitivity Reactions leading to treatment discontinuation,
xiv)	TEAE Classified as Infusion Related Reactions leading to treatment discontinuation,
xv)	TEAE Classified as Anaphylactic Reactions leading to treatment discontinuation,
xvi)	Serious TEAE Classified as Hypersensitivity Reactions leading to treatment discontinuation,
xvii)	Serious TEAE Classified as Infusion Related Reactions leading to treatment discontinuation,
xviii)	Serious TEAE Classified as Anaphylactic Reactions leading to treatment discontinuation,

All TEAEs will be summarized and presented in a listing for safety population.

9.1.2. Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are "Related" and "Not Related".

The drug-related TEAE data will be presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of TEAEs by CTCAE grade will be presented in a table. The possible severities are 'Mild', 'Moderate', 'Severe', 'Life-threatening' and 'Death related to AE'. In the TEAE severity table, if a subject reported multiple occurrence of the same TEAE, only the most severe will be presented.

The severity of the AE will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. A summary of TEAEs will be provided by treatment arm Adverse events will be presented by SOC, PT and CTCAE grade in a manner similar to that described in Section 9.1.1.

9.1.4. Serious Adverse Events

Treatment-emergent SAEs will be presented in a table. Drug Related treatment emergent SAEs will also be presented in a table.

The SAE data will be presented by SOC and PT in a manner similar to that described in Section 9.1.1. All SAEs will be summarized and presented in a listing for safety population.

9.1.5. Treatment-Emergent AEs Leading to Treatment Discontinuation

A summary of TEAEs with a study drug action taken of "Drug Withdrawn" will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. (Note that it is not expected that a subject would have more than one adverse event leading to discontinuation).

The TEAEs leading to treatment discontinuation will be presented by SOC and PT in a manner similar to that described in Section 9.1.1. All TEAEs leading to treatment discontinuation.

9.1.6. Treatment-Emergent Adverse Events Leading to Death

All subjects who have an AE leading to death will be presented in a listing for safety population.

9.1.7. Treatment-Emergent Adverse Events classified as Hypersensitivity Reactions

TEAEs recorded as hypersensitivity reactions in the eCRF will be included. Signs and symptoms of hypersensitivity reactions will be captured on separate eCRF pages. TEAEs classified as hypersensitivity reactions will be summarized as follows:

- Incidence of TEAEs classified as hypersensitivity reactions will be summarized as described in Section 9.1.1
- TEAEs classified as hypersensitivity reactions by causality will be summarized as described in Section 9.1.2
- TEAEs classified as hypersensitivity reactions by severity will be summarized as described in Section 9.1.3
- Serious TEAEs classified as hypersensitivity reactions by severity will be summarized as described in Section 9.1.3

All hypersensitivity reactions data will be summarized and presented in a listing for safety population.

9.1.8. Treatment-Emergent Adverse Events classified as infusion related reactions (IRR)

TEAEs classified as infusion related reactions (IRR) in the eCRF will be included. Signs and symptoms of IRRs data will be summarized as follows:

- Incidence of TEAEs classified as infusion related reactions (IRR) will be summarized as described in Section 9.1.1
- TEAEs classified as infusion related reactions (IRR) by severity will be summarized as described in Section 9.1.3
- Serious TEAEs classified as infusion related reactions (IRR) by severity will be summarized as described in Section 9.1.3

All IRRs data will be summarized and presented in a listing for safety population.

9.1.9. Treatment-Emergent Adverse Events classified as Anaphylactic Reactions

Anaphylactic Reactions is defined as per Section 6.3 in the protocol.

TEAEs classified as anaphylactic reactions in the eCRF will be included. Signs and symptoms of anaphylactic reactions data will be summarized as follows:

- Incidence of TEAEs classified as anaphylactic reactions will be summarized as described in Section 9.1.1
- TEAEs classified as anaphylactic reactions by severity will be summarized as described in Section 9.1.3
- Serious TEAEs classified as anaphylactic reactions by severity will be summarized as described in Section 9.1.3

All anaphylactic reactions data will be summarized and presented in a listing for safety population. In addition, summary of anaphylaxis criteria will be summarized and presented in listing for safety population.

9.2. Event of Special Interest (EOSI)

Any event of COVID-19 is to be considered as an "Event of Special Interest (EOSI). All EOSI classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0 or higher or available latest version).

All EOSI will be summarized and presented in a listing for the safety population.

9.2.1. Severity of Event of Special Interest (EOSI)

A summary of EOSI by CTCAE grade will be presented in a table. The possible severities are 'Mild', 'Moderate', 'Severe', 'Life-threatening' and 'Death related to AE'. In the EOSI severity table, if a subject reported multiple occurrence of the same EOSI, only the most severe will be presented.

The severity of the EOSI will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. A summary of EOSI will be provided by treatment arm Adverse events will be presented by SOC, PT and CTCAE grade in a manner similar to that described in Section 9.2

9.2.2. Serious Event of Special Interest (EOSI)

The Serious EOSI data will be presented by SOC and PT in a manner according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0 or higher or available latest version). All Serious EOSI will be summarized and presented in a listing for safety population.

9.2.3. Event of Special Interest (EOSI) Leading to Death

All subjects who have an EOSI leading to death will be presented in a listing for safety population.

9.3. Clinical Laboratory Evaluations

Clinical laboratory (biochemistry, hematology and urinalysis) test samples will be analyzed at the local laboratory. All summaries and listings will be presented in SI units.

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g. <0.5 will become 0.5) for summaries but left as recorded in the listing.

Actual value and change from baseline of all numeric laboratory parameters including clinical chemistry, hematology, urinalysis will be summarized using descriptive statistics in separate tables, by test parameter and visit.

The assessment at Day 1 and Day 15 for all the laboratory parameters will be conducted before the treatment administration.

All relevant clinical laboratory tests will be interpreted as below.

- Abnormal, Decreased, Clinically Significant
- Abnormal, Decreased, Not Clinically Significant
- Normal
- Abnormal, Increased, Clinically Significant
- Abnormal, Increased, Not Clinically Significant

These categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of subjects in that treatment within the safety population. Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of treatment is taken.

The numeric parameters will be graded using CTCAE v5.0, where applicable. The CTCAE grades for analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. Unit conversion will be performed if the clinical laboratory unit is not consistent with the unit in CTCAE v5.0. These grades will be summarized in shift tables comparing worst post baseline visit grade with those at the baseline visit.

The number and percentage of subjects will be summarized by CTCAE term and CTCAE grade for the safety population, where this summary includes only the most severe case during the overall post-baseline visits. All hematology, biochemistry and urinalysis data will be listed in separate listings along with clinical significance and normal range flags (where applicable) for the safety population.

9.3.1. Hematology

Hematology will be conducted at screening, on Day 1 (before treatment administration), Day 15 (before treatment administration), and at Weeks 4, 8, 12 (EOS/ET) and Week 26 visits. Hematology will include 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 (sec) and prothrombin time (%).

Neutropenia is defined based on CTCAE severity grade 1 as, an absolute neutrophil count (ANC) of less than 1500 per microliter (1500/microL). A summary table will be provided based on the safety population.

9.3.2. Biochemistry

Biochemistry will be conducted at screening, on Day 1 (before treatment administration), Day 15 (before treatment administration), and at Weeks 4, 8, and 12 (EOS/ET) and Week 26 visits. Biochemistry will include creatinine, blood urea nitrogen, fasting serum glucose, serum FSH (for postmenopausal women), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, albumin, chloride, calcium, phosphorous, uric acid, total protein, sodium, and potassium.

9.3.3. Urinalysis

Urinalysis will be conducted at screening, on Day 1 (before treatment administration), Day 15 (before treatment administration), and at Weeks 4, 8, and 12 (EOS/ET) and Week 26 visits. Urinalysis will include specific gravity, pH, protein, glucose, and blood.

9.4. Vital Sign Measurements

Vital sign will be conducted at screening, on Day 1, Day 15, and at Weeks 4, 8, 12 (EOS/ET) and Week 26 visits. At Day 1 and Day 15 the Vital signs will be assessed every 30 minutes (± 5 minutes) during and end of infusion at time points Pre-dose, 30 min, 1 hr, 1.5 hrs. 2 hrs, 2.5 hrs, 3 hrs, 3.5 hrs, 4 hrs, 4.5 hrs, 5 hrs, 5.5 hrs, 6 hrs, 6.5 hrs, 7 hrs, 7.5 hrs and 8 hrs.

A summary table with actual values and change from baseline will be presented for vital sign data (systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min) and oral temperature (^{0}C)) by scheduled visit and time point.

The indicative reference ranges for Systolic blood pressure: 90 – 140 mm Hg; Diastolic blood pressure: 50 – 90 mm Hg; Heart rate: 60 – 100 beats/min; Respiratory rate: 12 – 20 breaths/min; Temperature: 36 – 37.2 º C. Based on the ranges the parameters will be interpreted as below.

- Abnormal, Decreased, Clinically Significant
- Abnormal, Decreased, Not Clinically Significant
- Normal

- Abnormal, Increased, Clinically Significant
- Abnormal, Increased, Not Clinically Significant

A shift table comparing the interpretation at scheduled post-baseline visit and time point with those at baseline will be presented by visit and time point for the safety population.

All vital sign data will be listed by visit for safety population.

9.5. Physical Examination

Physical examinations will be performed at each visit. The body systems will be examined, and the findings will be classified as "Normal", "Abnormal, Not Clinically Significant" and "Abnormal, Clinically Significant". A shift table comparing the categorical results at each scheduled post-baseline visit with those at baseline will be summarized overall and by body system. All physical examination data will be listed by visit [Screening, Day 1 (Week 0), Day 15 (Week 0), Week 4, Week 8 Week 12 (EOS/EOT) and Week 26] and body system for safety population.

9.6. Electrocardiogram

12-lead ECGs will be performed at screening, Week 12 (EOS/ET) and Week 26 visits and interpreted as "Normal", "Abnormal, Not Clinically Significant" and "Abnormal, Clinically Significant". A shift table comparing the interpretation at scheduled post-baseline visit with those at baseline will be presented by visit for the safety population.

A summary table with actual values and change from baseline will be presented for ECG parameters (ventricular rate, P-R interval, QRS duration, Q-T interval, QTcF) by scheduled visit.

The reference ranges for Ventricular rate: 60 - 100 beats/min; P-R interval: 120 – 200 msec; QRS duration: 80 – 120 msec; QTcF: ≤ 450 msec. Based on the ranges the parameters will be interpreted as below.

- Abnormal Low
- Normal
- Abnormal High

All ECG data will be listed by visit for safety population.

9.7. Pregnancy Test

For subjects of childbearing potential, serum pregnancy test will be performed at screening, Week 12 EOS/ET and week 26 visit. A urine pregnancy test will be performed to confirm subjects are not pregnant on Day 1 prior to randomization and Day 15 before dosing and at week 2, week 4 and week 8 visits. The results will be classified as "Positive" or "Negative".
Serum pregnancy test results will be listed for safety population.

10. Changes in the Planned Analysis

10.1. Changes from Protocol

1. As per ICH E9 (R1), Estimand has been added in SAP based on client suggestion as per FDA requirement.

11. References

1. Dr. Reddy's Laboratories DRL_RI. Investigator Brochure.
2. Protocol version 3.0, Amendment 2 dated 10 Jul 2020.
3. MabThera (rituximab): Summary of Product Characteristics. Mar 25, 2020. Available at:https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf. Accessed June 22, 2020.
4. Rituxan (rituximab) Prescribing Information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103705Orig1s5458lbl.pdf Accessed July 02, 2020.
5. ICH Topic E 9 Statistical Principles for Clinical Trials September 1998. Available at:https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf.
6. Guideline for Industry: Structure and Content of Clinical Study Reports at: https://www.fda.gov/media/71271/download
7. Guideline of clinical investigation of medicinal products for the treatment of rheumatoid arthritis: December 14, 2019 at:https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-rheumatoid-arthritis_en.pdf
8. Guidance for Industry, Rheumatoid Arthritis at: :https://www.fda.gov/files/drugs/published/Rheumatoid-Arthritis--Developing-Drug-Products-for-Treatment.pdf
9. 12 Lead Electrocardiogram Reference Ranges: https://emedicine.medscape.com/article/2172196-overview

12. Appendices

12.1. Schedule of Study Procedures

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

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**			
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.

12.2. Tables and Listings

Tables:

Table No.	Table Title	Analysis Population
14.1.1.1	Summary of Screen Failures	All Subjects
14.1.1.2	Summary of Analysis Sets and Reason for Exclusion	All Randomized Subjects
14.1.1.3	Subject Disposition	All Randomized Subjects
14.1.1.4	Study Deviations	Safety Population
14.1.1.5	COVID-19 or Related Events Study Deviations	Safety Population
14.1.1.6	Missed Visit or Assessment Due to COVID-19 or Related Events	Safety Population
14.1.2.1	Demographics Baseline Characteristics	Safety Population
14.1.3.1	Baseline Disease Characteristics	Safety Population
14.1.4.1	Summary of Viral Serology	Safety Population
14.1.5.1	Summary of Medical and Surgical History	Safety Population
14.1.5.2	Summary of Rheumatic Disease History	Safety Population
14.1.6.1	Summary of Prior Medications	Safety Population
14.1.6.2	Summary of Concomitant Medications	Safety Population
14.1.6.3	Summary of Rescue Medications/Re-dosing Medications	Safety Population
14.1.7.1	Summary of Study Drug Administration	Safety Population
14.2.2.1	Summary of ADA and NaB by Visit and Overall	Immunogenicity Population
14.2.2.1A	Estimand 1: Summary of ADA and NaB by Visit and Overall	Immunogenicity Population
14.2.2.2	Summary of ADA titer by Visit	Immunogenicity Population
14.2.2.2A	Estimand 1: Summary of ADA titer by Visit	Immunogenicity Population
14.2.2.3	Shift from Baseline ADA Positive by Visit ADA Positive at Baseline	Immunogenicity Populations

14.2.2.3A	Estimand 1: Shift from Baseline ADA Positive by Visit ADA Positive at Baseline	Immunogenicity Populations
14.2.2.4	Summary of Time Matched Rituximab Concentration by Visit	TMRC Population
14.3.1.1	Overall Summary of Adverse Events	Safety Population
14.3.1.2.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.2.2	Study Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.2.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.4	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.2.5	Study Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.2.6	Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term	Safety Population
14.3.1.2.7.1	Treatment Emergent Adverse Events classified as Hypersensitivity Reactions by System Organ Class, Preferred Term and Relationship	Safety Population
14.3.1.2.7.2	Treatment Emergent Adverse Events classified as Hypersensitivity Reactions by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.7.3	Serious Treatment Emergent Adverse Events classified as Hypersensitivity Reactions by System Organ Class, Preferred Term and Relationship	Safety Population
14.3.1.2.7.4	Serious Treatment Emergent Adverse Events classified as Hypersensitivity Reactions by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.8.1	Treatment Emergent Adverse Events classified as Infusion Related Reactions (IRR) by System Organ Class, Preferred Term and Relationship	Safety Population

14.3.1.2.8.2	Treatment Emergent Adverse Events classified as Infusion Related Reactions (IRR) by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.8.3	Serious Treatment Emergent Adverse Events classified as Infusion Related Reactions (IRR) by System Organ Class, Preferred Term and Relationship	Safety Population
14.3.1.2.8.4	Serious Treatment Emergent Adverse Events classified as Infusion Related Reactions (IRR) by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.9.1	Treatment Emergent Adverse Events classified as Anaphylactic Reactions by System Organ Class, Preferred Term and Relationship	Safety Population
14.3.1.2.9.2	Treatment Emergent Adverse Events classified as Anaphylactic Reactions by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.9.3	Serious Treatment Emergent Adverse Events classified as Anaphylactic Reactions by System Organ Class, Preferred Term and Relationship	Safety Population
14.3.1.2.9.4	Serious Treatment Emergent Adverse Events classified as Anaphylactic Reactions by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.9.5	Treatment Emergent Adverse Events classified as Anaphylactic Reactions by Sampson's Anaphylaxis Criteria	Safety Population
14.3.1.2.10.1	Study Drug-Related Events of Special Interest (EOSI) by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.10.2	Study Drug-Related Serious Events of Special Interest (EOSI) by System Organ Class, Preferred Term and CTCAE Severity	Safety Population
14.3.1.2.11	Treatment Emergent Adverse Events for Rescue Medication by System Organ Class and Preferred Term	Safety Population
14.3.4.1.1	Actual Value and Change from Baseline in Hematology	Safety Population
14.3.4.1.2	Actual Value and Change from Baseline in Chemistry	Safety Population
14.3.4.1.3	Actual Value and Change from Baseline in Urinalysis	Safety Population
14.3.4.1.4	Summary of Neutropenia	Safety Population

14.3.4.2.1.1	Shift from Baseline in Hematology	Safety Population
14.3.4.2.1.2	Hematology Shift Table Based on CTCAE Grade by Parameter	Safety Population
14.3.4.2.2.1	Shift from Baseline in Biochemistry	Safety Population
14.3.4.2.2.2	Biochemistry Shift Table Based on CTCAE Grade by Parameter	Safety Population
14.3.4.2.3	Shift from Baseline in Urinalysis	Safety Population
14.3.4.3.1	Actual Value and Change from Baseline in Vital Signs	Safety Population
14.3.4.3.2	Shift from Baseline in Vital Signs	Safety Population
14.3.4.4	Shift from Baseline in Physical Examination	Safety Population
14.3.4.5.1	Actual Value and Change from Baseline in 12-Lead Electrocardiogram	Safety Population
14.3.4.5.2	Shift from Baseline in Overall 12-Lead Electrocardiogram	Safety Population
14.3.4.5.3	Shift from Baseline in 12-Lead Electrocardiogram by Parameter	Safety Population
14.3.4.5.4	Pregnancy Test (Women of Childbearing Potential)	Safety Population

Listings:

Listing No.	Listing Title	Analysis Population
16.2.1.1	Screen Failures	All Subjects
16.2.1.2	Randomization	Safety Population
16.2.1.3.1	Disposition	All Randomized Subjects
16.2.1.3.2	Disposition	All Randomized Subjects
16.2.1.4	Analysis Sets	All Randomized Subjects
16.2.2.1	Study Deviations	Safety Population
16.2.2.2	COVID-19 Related Study Deviations	Safety Population
16.2.2.3	Missed Visit or Assessment Due to COVID-19	Safety Population
16.2.2.4	COVID-19 or Related Events Study Disruptions	Safety Population
16.2.2.5	COVID-19 Testing	Safety Population
16.2.4.1	Demographics and Baseline Characteristics	Safety Population
16.2.4.2	Baseline Disease Characteristics	Safety Population
16.2.4.3	Viral Serology at Screening	Safety Population
16.2.4.4	Tuberculosis Monitoring (TB)	Safety Population
16.2.4.5	Serum IgG and IgM Assessments	Safety Population
16.2.4.6	Medical and Surgical History	Safety Population
16.2.4.7	Rheumatic Disease History	Safety Population
16.2.4.8	Inclusion and Exclusion Criteria Deviation	All Enrolled
16.2.4.9	Prior Medications	Safety Population
16.2.4.10	Concomitant Medications	Safety Population
16.2.4.11	Pre-Medication	Safety Population
16.2.4.12	Rescue Medications/Re-dosing Medications	Safety Population
16.2.5.1	Study Drug Administration I	Safety Population
16.2.5.2	Study Drug Administration II	Safety Population
16.2.6.1	ADA, Nab and Titer	Immunogenicity Population
16.2.6.2	Time Matched of Rituximab Concentration	TMRC Population

16.2.7	All Non-Treatment Emergent Adverse Events	Safety Population
16.2.7.1	All Treatment Emergent Adverse Events	Safety Population
16.2.7.2	Treatment Emergent Serious Adverse Events	Safety Population
16.2.7.3	Treatment Emergent Adverse Events by Relationship	Safety Population
16.2.7.4	All Treatment Emergent Adverse Events Leading to Treatment Discontinuation	Safety Population
16.2.7.5	All Treatment Emergent Adverse Events Leading to Death	Safety Population
16.2.7.6	All Treatment Emergent Adverse Events Classified as Hypersensitivity Reactions	Safety Population
16.2.7.7	All Treatment Emergent Adverse Events Classified as Anaphylactic Reactions	Safety Population
16.2.7.8	All Treatment Emergent Adverse Events Classified as Infusion Related Reactions (IRR)	Safety Population
16.2.7.9	Events of Special Interest (EOSI)	Safety Population
16.2.7.10	Serious Events of Special Interest (EOSI)	Safety Population
16.2.7.11	All Treatment Emergent Adverse Events Attributable for Rescue Medication	Safety Population
16.2.8.1	Laboratory Results – Hematology	Safety Population
16.2.8.2	Laboratory Results – Biochemistry	Safety Population
16.2.8.3	Laboratory Results – Urinalysis	Safety Population
16.2.9.1	Vital Signs	Safety Population
16.2.9.2	Physical Examination	Safety Population
16.2.9.3	12-Lead Electrocardiogram	Safety Population
16.2.9.4	Pregnancy Test	Safety Population

Statistical Analysis Plan (SAP) Client Approval Form

Client:	Dr. Reddy's Laboratories S.A.
Protocol Number:	RI-01-007
Document Description:	Final Statistical Analysis Plan
SAP 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®
SAP Version Number:	2.0
Effective Date:	CI [redacted]

CI [redacted]

Approved by:

CI [redacted]