A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma

ClinicalTrials.gov Identifier: NCT03976102

Date of Protocol: 27 October 2021

Title Page

Protocol Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma

Protocol Number: RI-01-006

Amendment Number: 4

Compound Number: DRL_RI

Short Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma

Sponsor Name and Legal Registered Address: Dr. Reddy's Laboratories S.A.
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Regulatory Agency Identifying Number(s): Investigational New Drug (IND) number: 112766

Version number: 5

Approval Date: 27 Oct 2021

Date and Version of Previous Protocol: 04 Nov 2020, Version 4.

The confidential information in this document is provided to you as an Investigator, potential Investigator or consultant for review by you, your staff, and applicable Independent Ethics Committee and/or Institutional Review Board. It is understood that the information will not be disclosed to others without written authorisation from Dr. Reddy's Laboratories S.A. except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

Sponsor Signature Page

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice (GCP) applicable to this clinical study.

Sponsor Signatory:

PPD

PPD

Date

PPD

Key Study Personnel

Sponsor	Dr. Reddy's Laboratories S.A. Elisabethenanlage 11 CH-4051 Basel Switzerland
Contract Research Organisation	PPD
Adverse Event Reporting	PPD
Medical Monitors	PPD
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Central Histopathology Laboratory	PPD
Bioanalytical Laboratories	PPD

	PPD

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Amendment 4	Protocol Version 5	27 Oct 2021
Amendment 3	Protocol Version 4	04 Nov 2020
Amendment 2	Protocol Version 3	04 Dec 2019
Amendment 1	Protocol Version 2	04 Jan 2019
Original Protocol	Protocol Version 1	25 Oct 2018

Amendment 4,

Overall Rationale for the Amendment

This amendment allows the incorporation of various measures taken to adapt for conduct of the clinical study in the Coronavirus disease pandemic situation including adaptations of the study results analysis based on the discussions with the United States Food and Drug Administration during Biological Product Development type 2 meeting held on 02 Jul 2021.

The changes from the previous version of the protocol are summarised in a tabulated manner below.

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
1.	**Key Study Personnel; Medical Monitors**	PPD	PPD	To align with updated list of medical monitors.
2.	**Section 1.1, Synopsis**	-	The Synopsis reflects changes made in various sections of the protocol	To align with changes made in various sections of the protocol
3.	**Section 1.2, Schema**	N=up to 284*	**N=Approximately 312**	Number of subjects to be randomised is updated to 312 based on the revision in the sample size calculation assumptions and blinded sample size re-estimation.
4.	**Section 3, Objectives and Endpoints** **Primary objective**	Objective: To demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by ORR at Week 28, evaluated in accordance with published response criteria for malignant lymphoma.	Objective: To demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by overall response (ORR) **up to** Week 28, evaluated in accordance with published response criteria for malignant lymphoma.	Editorial change in the objective based on the revision in the primary endpoint.
5.	**Section 3, Objectives and Endpoints** **Primary endpoints** **Section 4.1.1, Description** **Section 8.2, Efficacy assessments** **Section 9.4.1.1,** Analysis of Primary efficacy endpoint	End point: The primary endpoint is ORR, defined as the proportion of subjects in each treatment group that achieve CR, CRu or PR at Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma.	Endpoint: The primary endpoint is **B**ORR, defined as the proportion of subjects in each treatment group that achieve **a best overall response of either** CR, CRu or PR **up to** Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma.	Change in the endpoint based on the discussions with United States Food and Drug Administration during

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
				Biological Product Development type 2 meeting held on 02 Jul 2021.
6.	**Section 3, Objectives and Endpoints** **Secondary objectives and endpoints**	Objective: To compare the ORR at Week 12, CR at Week 28 duration of response (DOR), PFS and OS of DRL_RI with MabThera® in subjects with CD20 positive, LTB FL End point: Overall response rate at Week 12 based on central radiology review in accordance with published response criteria for malignant lymphoma.	Objective: To compare the ORR at Week 12 **and Week 28**, CR at Week 28, **CR as a best response up to week 28**, duration of response (DOR), PFS and OS of DRL_RI with MabThera® in subjects with CD20 positive, LTB FL Endpoint**:** Overall response rate at Week 12 and W**eek 28** based on central radiology review in accordance with published response criteria for malignant lymphoma. • **Complete Response (CR) rate as a best response up to Month 7 (Week 28).**	Addition of ORR at Week 28 and CR rate as a best response up to Month 7.
7.	**Section 4, Study design**	It is planned to randomise 284 subjects (to be reconfirmed under blinded conditions on the basis of the observed ORR and drop-out rate) at approximately ≥130 study sites worldwide.	It is planned to **randomise approximately 312 subjects** at approximately ≥130 study sites worldwide.	Number of subjects to be randomised is updated to 312 based on the revision in the sample size calculation assumptions and blinded sample size re-estimation.
8.	**Section 4.5, End of Study Definition**	Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, and urinalysis.	Clinical laboratory tests: Blood and urine samples will be taken for haematology, **coagulation**, biochemistry, and urinalysis **Viral disease screening at the EOS Visit** **COVID-19 questionnaire.**	Editorial changes to keep the section consistent with the Schedule

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
				of assessments (SoA)
9.	**Section 9, Statistical Considerations**		**9.1.3 Inter-current events due to COVID-19: Handling (i.e., analysis and presentation) of intercurrent events and data/visit impacted due to COVID-19 pandemic will be described in the SAP. The following events are considered as inter-current events due to COVID-19 pandemic and any study data missing as an outcome of these events will be handled as missing data impacted due to COVID-19.** - **COVID-19 infection or death due to COVID-19 (as an Event of Special Interest)** - **Protocol deviation including missing assessment due to COVID-19 pandemic** **Any other documented event which may interfere the study conduct and is reasonable related to COVID- 19 pandemic** **Full details of the COVID 19 related inter-current events definitions will be provided in SAP.**	Addition of inter-current events based on the discussions with United States Food and Drug Administration during Biological Product Development type 2 meeting held on 02 Jul 2021.
10.	**Section 9.2, Sample size determination**	Published data for rituximab versus watch and wait[9] revealed [redacted] CCI [redacted]	**Published data for rituximab versus a "watch and wait" strategy in the first line treatment of LTBFL (Ardeshna et al 2014) revealed** [redacted] CCI [redacted]	Based on the revised sample size justification and blinded sample size re-estimation, there is revision in the sample size.

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
		[redacted] CCI [redacted]	[redacted] CCI [redacted]	

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
			[redacted] CCI [redacted] **Based on the observed pooled best overall response (BOR) rate, up to week 28, the revised total sample size obtained in the BSSR is 312 subjects (156 per group) to be recruited.**	
11.	**Section 9.3.2, Per Protocol Population**	The PP Population will include all subjects who are randomised into the study, receive at least one dose of study drug (sufficient compliance to be evaluated under blind conditions), have measurable disease at Baseline as	The PP Population will include all subjects who are randomised into the study, receive at least one dose of study drug (sufficient compliance to be evaluated under blind conditions), have measurable disease at Baseline as confirmed by central review, have an **at least one** available valid response evaluation **up to**	Revision in the text for better clarity and as per the other changes made in endpoints.

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
		confirmed by central review, have an available valid response evaluation at 7 months (+, and no major protocol deviations (such as administration of a forbidden treatment) that would significantly impact the primary efficacy endpoint. If the forbidden treatment was administered due to PD, the subject will be included in the PP Population as a non-responder. In the EMA analysis, both ITT and PP population will be considered as primary.	7 months **(± 4 weeks)**, and no major protocol deviations (such as administration of a forbidden treatment) that would significantly impact the primary efficacy endpoint. If the forbidden treatment was administered due to PD, the subject will be included in the PP Population as a non-responder. In the EMA analysis, both ITT and PP population will be considered as primary.	
12.	**Section 9.4.1.1, Analysis of Primary Efficacy Endpoint**	Equivalence will be concluded for FDA if the 90% CI and for EMA if the 95% CI of the ORR difference is completely contained within the pre-defined interval (-16%, 16%). [redacted] CCI [redacted]. Full details of the primary endpoint analysis including multiplicity considerations will be provided in the SAP.	Equivalence will be concluded for FDA if the 90% CI and for EMA if the 95% CI of the ORR difference is completely contained within the pre-defined interval **(- 17%, 17%)**. [redacted] CCI [redacted] Full details of the primary endpoint analysis including multiplicity considerations will be provided in the SAP.	Updated in the equivalence margin based on the changes made in the **9.2, Sample size determination**
13.	**Section 9.4.2, Safety Analyses**	TEAEs will be described using descriptive statistics and coded according to the MedDRA (version 21.1 or latest) system organ class and MedDRA preferred term, graded according to	TEAEs including **Event of Special Interest (COVID-19 infection or death due to COVID-19 infection)** will be described using descriptive statistics and coded according to the MedDRA (version 21.1 or latest) system organ class and MedDRA preferred term,	Inclusion of text regarding COVID-19 events based on the earlier changes

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
		CTCAE version 5.0, by treatment group and overall. TEAEs observed, based on the onset date, during the rituximab induction and maintenance will be summarised separately by treatment group. Drug-related TEAEs and SAEs, TEAEs leading to study discontinuation, and death will also be summarised by treatment group and overall.	graded according to CTCAE version 5.0, by treatment group and overall. TEAEs observed, based on the onset date, during the rituximab induction and maintenance will be summarised separately by treatment group. Drug-related TEAEs and SAEs, TEAEs leading to study discontinuation, and death will also be summarised by treatment group and overall.	belongs to addition of inter-current events.
14.	**Section 9.4.7, Reporting Timeframes**	When all subjects have completed Week 28 (or the EOS/ET Visit for subjects discontinued prior to Week 28), the primary endpoint (ORR at Week 28) will be analysed using centrally reviewed radiology assessments and a study report produced. Available safety data and other secondary and exploratory endpoints may also be reported at that time including ORR at Week 12. An addendum study report will be provided to applicable regulatory authority when all subjects have completed the study, including updated safety data and secondary endpoints for time to event endpoints. Further details will be provided in the SAP.	When all subjects have completed Week 28 (or the EOS/ET Visit for subjects discontinued prior to Week 28), the primary endpoint (**B**ORR **up to** Week 28) will be analysed using centrally reviewed radiology assessments and a study report produced. Available safety data and other secondary and exploratory endpoints may also be reported at that time including ORR at Week 12 **and Week 28**. An addendum study report will be provided to applicable regulatory authority when all subjects have completed the study, including updated safety data and secondary endpoints for time to event endpoints. Further details will be provided in the SAP.	Editorial changes based on the revisions made to other sections

S. No.	Section Number and Name	Previous Protocol V4.0 dated 04 November 2020	Current Protocol V5.0 dated 27 October 2021	Brief Rationale
15.	**General**	-	Abbreviations, grammar/typo-error were corrected as applicable	For better clarity.

Table of Contents

List of Tables

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma

Sponsor Study No.: RI-01-006

Phase: III

Sponsor: Dr. Reddy's Laboratories S.A.

Rationale: The evaluation of pharmacokinetics (PK), efficacy, and safety (including immunogenicity assessment) between a proposed biosimilar and the reference medicinal product (RMP) is an essential component of an efficient clinical study program collectively providing the evidence of biosimilarity. Results from a previous study CCI [redacted] show that the 91% confidence interval (CI) for the test-to-reference ratios of all pre-specified primary and secondary PK endpoints were within the pre-specified window of 80.00% to 125.00% for the comparisons of proposed rituximab biosimilar (DRL_RI) to MabThera® and Rituxan®, and for the comparison of MabThera® to Rituxan®, demonstrating the PK similarity of the 3 products.

The primary objective of the current study is to demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with cluster of differentiation 20 (CD20)-positive, low tumour burden follicular lymphoma (LTB-FL) in the first line treatment setting, as measured by overall response rate (ORR). While the use of rituximab monotherapy as first-line treatment of LTB-FL is not approved in the United States (US) or European Union (EU), it is frequently used and has the potential to replace watch and wait as the treatment of choice for asymptomatic, LTB-FL.

Objectives and Endpoints

Objective	Endpoint
Primary	
• To demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by ORR up to Week 28, evaluated in accordance with published response criteria for malignant lymphoma	• The primary endpoint is BORR (best overall response rate), defined as the proportion of subjects in each treatment group that achieve a best overall response of either complete response (CR), unconfirmed complete response (CRu) or partial response (PR) up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma. [13]
Secondary	
• To compare the ORR at Week 12 and Week 28, CR at Week 28, CR as a best response up to week 28, duration of response (DOR), PFS and OS of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL	• Overall response rate at Week 12 and Week 28 based on central radiology review in accordance with published response criteria for malignant lymphoma.[13] • Complete Response (CR) rate at Month 7 (Week 28). • CR rate as a best response up to Month 7 (Week 28). • Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS. • Progression-free survival defined as the time from date of randomisation to the date of documented progressive disease (PD) or death due to any cause. • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/End of Study (EOS).
• To compare the safety, tolerability, and immunogenicity of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL.	• Adverse events (AE), clinical laboratory values, vital signs, and electrocardiogram (ECG) • Anti-rituximab antibodies and their relationship with other outcome measures.

Exploratory	
• To compare ORR evaluated in accordance with the Lugano criteria [14] in subjects with CD20-positive, LTB-FL treated with either DRL_RI or MabThera®.	• Overall response rate based on the Lugano criteria [14] for those subjects with available positron emission tomography (PET) data.
• To explore the PK parameters of DRL_RI and MabThera®, using a population-PK modelling approach. • To explore the pharmacodynamic parameters of DRL_RI and MabThera®.	• Pharmacokinetic parameters (e.g., clearance and volume of distribution) for DRL_RI and MabThera® will be derived using a population-PK modelling approach. • Potential differences in pharmacodynamic parameters (e.g., area under the effect curve [AUEC] of circulating B-cells depletion) for DRL_RI and MabThera® will be investigated.

Overall Design:

This is a randomised, double-blind, parallel-group, equivalence, multicentre Phase III study. The study will consist of a Screening Period (Days -35 to -1), a 4-week Induction Treatment Period (Day 1 [Week 1] to Week 4), a Maintenance Treatment Period (Week 12 to Week 36) and Follow-up Period (Week 44 and 52).

It is planned to randomise approximately 312 subjects as per the Blinded Sample Size Re-estimation (BSSR) result, (please refer Section 9.2) at approximately ≥130 study sites worldwide.

It is planned to randomise approximately 312 subjects with CD20-positive, LTB-FL will be randomised to receive either DRL_RI or MabThera®. Subjects will receive induction treatment consisting of a weekly intravenous (i.v) infusion for 4 weeks (375 mg/m^2 of body surface area [BSA]) followed by maintenance treatment consisting of an i.v infusion (375 mg/m^2 of BSA) every 8 weeks starting at Week 12 until Week 36. After completion of the Maintenance Treatment Period, subjects will be followed up until 52 weeks after the first dose of study drug (at Weeks 44 and 52).

Randomisation will be stratified by low-, medium-, and high-risk subjects using the [redacted] CCI [redacted], as well as by tumour grade (1-2 Vs. 3a; i.e., subjects with Grade 1 tumours should be pooled with those with Grade 2 tumours, resulting in 2 levels for this factor) and geographical area (USA, Europe and Asia Pacific region).

Subjects will attend study visits every week (±2 days) during the Induction Treatment Period (Weeks 1 to 4), at Week 8 (±7 days), thereafter every 8 weeks (±7 days) from Week 12 until Week- 52 (EOS/Early termination [ET] Visit). Study procedures include physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, tumour assessments, clinical laboratory tests, serum lactate dehydrogenase (LDH) and β-2 microglobulin, coronavirus disease 2019 (COVID-19) testing at screening and as deemed appropriate by the Investigator at any time during the study, AEs, concomitant medication, immunogenicity, and PK and pharmacodynamic samplings for the subjects in the corresponding subset.

All subjects completing the study (Week 52) will attend an EOS Visit. Subjects discontinuing the study before Week 52 for any reason will also attend an ET Visit.

Subjects with a prior history of hepatitis B infection or with serological tests suggestive of previous hepatitis B infection will continue to receive hepatitis B virus (HBV) antiviral prophylaxis therapy for at least 12 months post last dose of rituximab in the study and will be monitored and reported for reactivation for up to 24 months following completion of rituximab therapy.

Subjects prematurely discontinued from treatment, but wishing to continue in the study, will return for an ET Visit 8 weeks after the last dose of study drug. The post-treatment discontinuation follow-up for subjects wishing to continue in the study is detailed below:

If the reason for study discontinuation is disease progression, the subjects will be contacted by telephone for information on survival, AEs, and concomitant medications every 8 weeks, for a total observation period of 52 weeks.

If the reason for study discontinuation is different from disease progression, subjects will continue to attend scheduled tumour assessments (at which AE and concomitant medication information will also be collected) up to disease progression or Week 52, whichever occurs first. If these subjects subsequently experience disease progression, then they will continue to be followed up by telephone every 8 weeks from that point of identification and for a total observation period of 52 weeks, as described for subjects discontinued from study drug due to disease progression.

Clinical assessments will be performed before the start of each treatment cycle by the Investigator. Tumour assessments for the purpose of assessing subject eligibility (with central imaging confirmation) and medical care will be performed by the investigational site at Screening and Weeks 12, 28, and 52 (EOS/ET Visit).

Number of Subjects:

Based on the observed pooled best overall response (BOR) rate, up to week 28, the revised total sample size obtained during the BSSR is approximately 312 subjects (156 per group) to be recruited.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

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

1. Signed written informed consent.
2. Male or female subjects aged ≥18 years of age.
3. Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per Groupe D'Etude des Lymphomes Folliculaires (GELF) based criteria. Subjects must have sufficient tissue samples available for the central pathology review (Section 8.1.1), and a centrally-confirmed diagnosis prior to being randomised. Should a subject be eligible as per the central imaging review but not as per the Study Centre Review the subject will be considered eligible if confirmed both by the Investigator and the Medical Monitor. For any other disagreement in eligibility the subject will be considered ineligible.
4. Ann Arbor Stage II to IV.
5. ECOG status of 0 to 1.
6. Low tumour burden follicular lymphoma defined as:
    - As per central radiological assessment, nodal or extranodal mass involvement with diameter measuring <7 cm
    - As per central radiological assessment, involvement of ≤3 nodal sites with diameter measuring >3 cm
    - Absence of systemic symptoms or B-symptoms* (asymptomatic)

      *B-symptoms defined as weight loss >10% within last 6 months, recurrent or continuous night sweats, intermittent or continuous fever recorded as axillary or oral temperature >38°C for at least 3 days
    - As per central radiological assessment, absence of splenomegaly (defined as spleen size higher than 16 cm by computed tomography [CT] scan)

- Absence of risk of vital organ compression based on clinical finding
- Absence of leukemic phase (leukemic phase defined as a count >5,000/µL of circulating tumour cells)
- Absence of clinically significant cytopenias (defined as a platelet count of <100,000/µL, haemoglobin <10 g/dL, or absolute neutrophil count <1,500/µL)
- Absence of clinically significant serous effusion based on clinical examination and CT scan
- Serum LDH not higher than the upper limit of normal (ULN) by local laboratory.

7. Subject has at least 1 measurable tumour mass in 2 dimensions as per central radiological assessment, and the mass must be:
    - Nodal lesion >15 mm in the longest dimension; or
    - Nodal lesion >10 mm to ≤15 mm in the longest dimension and >10 mm in the shortest dimension; or
    - Extranodal lesion with both long and short dimensions ≥10 mm.
8. Creatinine clearance ≥45 mL/min as calculated by the Cockcroft-Gault method.
9. Aspartate transaminase, alanine transaminase, alkaline phosphatase values ≤3 × ULN, total or conjugated bilirubin values ≤1.5 × ULN.
10. Life expectancy ≥3 months.
11. Able to comply with the study protocol.
12. If female subject, then subject should be non-pregnant, non-lactating. Adequate contraception or post-menopausal/non-childbearing status (e.g., women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history). Women of childbearing potential must practice effective birth control for the duration of the study and for 12 months after the last study drug dose. For this same duration, male subjects participating in the study should avoid passing the semen to female partners during sexual intercourse.

Exclusion Criteria

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

1. Prior use of rituximab or any CD20 monoclonal antibody for any reason.
2. Any contraindication to the use of rituximab.

3. Any prior therapy for follicular lymphoma (including but not limited to chemotherapy, radiotherapy).
4. Subjects who, in the opinion of the Investigator, require additional concomitant treatment for lymphoma.
5. Evidence of histologic transformation to high grade lymphoma or diffuse large B-cell lymphoma.
6. Known Central Nervous System (CNS) involvement by lymphoma. (Note: CNS imaging is not required unless clinically indicated).
7. Subjects on chronic supra-substitutive doses (defined as doses in excess of 7.5 mg per day of prednisone or prednisone equivalent for a period longer than 3 weeks) of systemic glucocorticoids.
8. Prior malignancy (including recurrence) within 5 years of screening, other than non-melanoma skin cancer or intraepithelial cervical neoplasia, successfully treated more than 1 year before study inclusion.
9. Subjects with known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV).
10. Subjects with positive serological test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C virus (HCV) antibody can only be included in the study if any of the following is fulfilled. [18,19]
    a. Subjects with a negative HBsAg and positive total HBcAb must have a HBV deoxyribonucleic acid (DNA) level <20 IU/mL (or 112 copies/mL) by polymerase chain reaction (PCR) to participate in the study. In addition, it is required for these subjects to follow consultation with a Hepatologist / relevant expert regarding initiation, monitoring, and use of HBV antiviral therapy and the subject must be willing to undergo PCR HBV DNA testing during treatment and agree to receive treatment as indicated. HBV DNA re-test will be performed as per the schedule of assessments (see Table 1–1) and further as needed, at the discretion of the Investigator.
    b. Subjects with a positive test because of HBV vaccination may be included (i.e., HBsAg negative, anti-HBs+, HBcAb–).
    c. Subjects positive for HCV antibody are eligible only if the PCR test for HCV ribonucleic acid (RNA) is negative.

11. 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 drug (Day 1). If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.
12. Subjects who have received a live vaccine within last 3 months or non-live vaccine within 4 weeks of the first administration of study drug. *[Note: A need may arise for trial subjects to receive vaccine against COVID-19 while being a part of the study. All such decisions will be taken at the discretion of the Investigator in consultation with the CRO / Sponsor after due consideration to subjects' safety, national health policy of the respective country and overall need by the subject for such vaccine during the time of study participation]*.
13. Subjects with an active uncontrolled infection requiring systemic treatment at Screening or history of documented recurrent clinically significant infection within 6 months of study inclusion (e.g., 2 or more viral, bacterial or fungal infections requiring in-patient treatment).
14. Subjects with New York Heart Association (NYHA) class III or IV congestive heart failure or relevant arrhythmia or angina based on ECG with clinical judgment.
15. Subjects with known hypersensitivity to rituximab or its excipients, or to proteins of murine or other foreign origin.
16. History or presence of a medical condition or disease that in the Investigator's opinion would place the subject at an unacceptable risk for study participation.
17. Participation in any clinical study or having taken any investigational therapy during the 2-month period immediately preceding administration of the first dose of study drug.
18. Lactating or pregnant female.
19. Women of childbearing potential who do not consent to use highly effective methods of birth control (e.g., sterilisation, or other non-hormonal forms of contraception) during treatment and for at least 12 months after the last administration of study drug. True abstinence periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
20. Subject has been previously randomised in this study.
21. Subject likely not to be available to complete all protocol required study visits or procedures.

Treatment Groups and Duration:

The study drug DRL_RI or MabThera® will be administered as an i.v infusion, at a dose of 375 mg/m^2 of BSA. Subjects will receive induction treatment consisting of weekly i.v infusions up to Week 4 followed by maintenance treatment consisting of an i.v infusion every 8 weeks from Week 12 up to Week 36. Subjects will be pre-medicated before each infusion with acetaminophen, diphenhydramine, and 100 mg i.v methylprednisolone or their equivalent to decrease the incidence and severity of acute infusion-related reactions (IRRs).

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 every 30 minutes, to a maximum of 400 mg/hour.

Subsequent Infusions: 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.

Infusions should be administered under close medical supervision. The infusion should be interrupted, or the infusion rate slowed for infusion reactions. If symptoms improve, the infusion rate can be continued at one-half the previous rate.

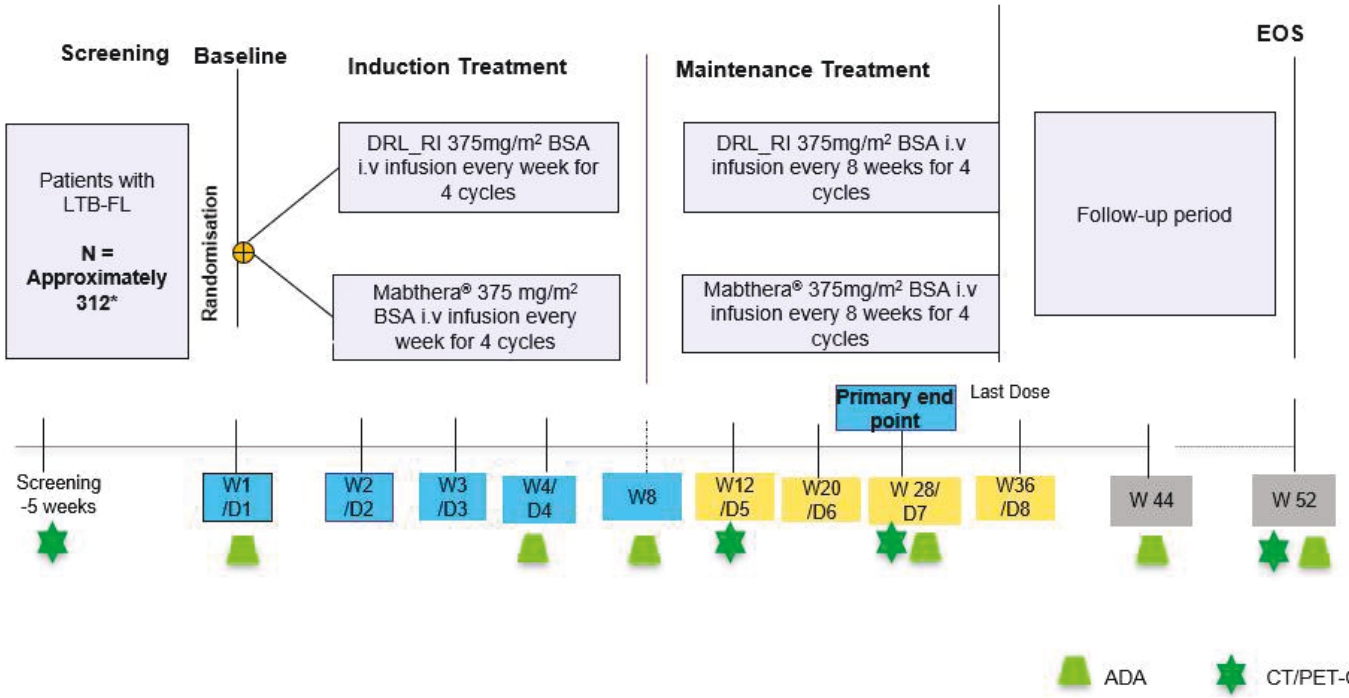
Whenever the infusion is interrupted, the stop time and restart time should be recorded (with date, hour and minutes) along with initial start and final end time. Rates of infusion throughout should be recorded.

The preparation of rituximab infusion for dosing must be handled by the trained study personnel who is an unblinded team member and not part of any other study assessments. The study drugs should be kept in a secure area with access limited to authorised persons.

An unblinded team shall be responsible for maintaining drug accountability logs and unblinded clinical site manager (CSM) will verify the same as part of monitoring visits.

A separate unblinded team at the Contract Research Organisation (CRO) and site level will manage the shipping, inventory, storage, accountability and dosing preparation of the study drug.

1.2 Schema



Abbreviations: ADA = anti-drug antibodies; BSA = body surface area; CT = computerized tomography; D = Dose; CCI [redacted] i.v = intravenous; H = high; L = low; LTBFL = low tumour burden follicular lymphoma; M = medium; W = week; PET = positron emission tomography ; PK =pharmacokinetic

1.3 Schedule of Activities

An overview of the protocol visits and procedures is provided in Table 1–1. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may 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. Unscheduled visits (including reason) will be collected in the electronic case report forms (eCRF).

The following priority order will be in effect when more than one assessment is required at a time point:

1. 12-lead ECG
2. Vital signs
3. Pharmacokinetic blood sampling (subjects included in the PK and pharmacodynamic subset only)
4. Pharmacodynamic blood sampling (subjects included in the PK and pharmacodynamic subset only)
5. Blood sampling for safety assessments

Table 1–1 Schedule of Assessments

Visit	Screening	Induction Treatment Period					Maintenance Treatment Period	Follow-up Period	
		Baseline	Week (Day) ± 2 days			Week ± 7 days	Week ± 7 days	Week ± 7 days	EOS/ET[1] Week ± 7 days
Timing	**Days -35 to -1**	**Days 0 to 1[2]**	**2 (8)**	**3 (15)**	**4 (22)**	**8**	**12, 20, 28, 36**	**44**	**52**
Baseline[3]		X							
Informed consent[4]	X								
Inclusion/exclusion criteria[5]	X	X							
CCI criteria	X								
Histological confirmation of diagnosis[6]	X								
Medical, surgical and oncology history including medications	X								
Demographics	X								
Physical examination[7]	X	X	X	X	X	X	X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X
Pregnancy test[9]	X	X	X	X	X		X		X
ECOG performance status	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[10]	X	X	X	X	X	X	X	X	X
LDH and β-2 microglobulin	X	X	X	X	X	X	X	X	X
TB screening[11]	X								
Viral disease screening[12]	X						X[12]	X[12]	X[12]
12-Lead ECG	X								X

Visit	Screening	Induction Treatment Period					Maintenance Treatment Period	Follow-up Period	
		Baseline	Week (Day) ± 2 days			Week ± 7 days	Week ± 7 days	Week ± 7 days	EOS/ET[1] Week ± 7 days
Timing	**Days -35 to -1**	**Days 0 to 1[2]**	**2 (8)**	**3 (15)**	**4 (22)**	**8**	**12, 20, 28, 36**	**44**	**52**
CT Scan[13] or [^{18}F]FDG-PET/PET-CT[14]	X						X[13,14]		X
Bone marrow biopsy[15]	X						X[15]		X[15]
Randomisation		X[16]							
Study drug administration[17]		X	X	X	X		X		
PK sampling[18]		X	X	X	X		X[18]		
Pharmacodynamic sampling[19]		X	X	X	X		X[19]	X	X
Immunogenicity[20]		X			X	X	X[20]	X	X
Adverse events including IRR	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
COVID-19 testing[21]		X							
COVID-19 related screening questionnaire	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BAb = binding antibodies; COVID-19 = Coronavirus disease 2019; C_{trough} = trough plasma concentration; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS/ET = End of Study/Early Termination; [^{18}F]FDG-PET: fluorine-18-fluorodeoxyglucose positron emission tomography; FL = follicular lymphoma; CCI CCI ; HBV = hepatitis B virus; HCV = hepatitis C virus; IRR = infusion-related reactions; IWRS = interactive web response system; LDH = lactate dehydrogenase; NAb = neutralising antibodies; PET-CT = positron emission tomography - computed tomography; PK = pharmacokinetic; PR = partial response; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; TB = tuberculosis.

1. All subjects completing the study (Week 52) and those discontinuing the study at any time for any reason will attend the EOS Visit. Subjects experiencing disease progression will discontinue study drug and attend the ET Visit, which is to be scheduled 8 weeks after the last dose of study drug administration. These subjects will then be contacted by telephone for information on survival, AEs, and concomitant medications every 8 weeks, for a total observation period of 52 weeks. Subjects who wish to remain in the study but withdraw from the study drug for any reason other than disease progression will return for an ET Visit 8 weeks after the last dose of study drug and continue to attend scheduled tumour assessments (at which AE and concomitant medication information will also be collected) up to disease progression or Week 52, whichever occurs first. Note: if these subjects subsequently experience disease progression then they will continue to be followed up by telephone every 8 weeks from that point of identification and for a total observation period of 52 weeks, as described for subjects discontinued from study drug due to disease progression.
2. Day 0 and Day 1 can be clubbed into one single day. However, randomisation in IWRS and administration of first dose of study medication should take place on the same day and this will be considered as Day 1.
3. If the assessment is repeated before dosing, then latest values/observations will be considered as Baseline value/observation.
4. Informed consent must be obtained prior to undergoing any study-specific procedure.
5. All eligibility criteria must be met based on the screening assessment before a subject is randomised to study drug. Subjects that do not meet all requirements can be rescreened at the Investigator's discretion, following discussion with the Sponsor/designee Medical Monitor.
6. Subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site. Subjects must have sufficient tissue samples available for the central pathology review (obtained on or within 12 months prior to the screening date) and a centrally-confirmed diagnosis prior to being randomised.
7. Complete physical examinations, including a thorough assessment of the lymph nodes, liver, and spleen, will be conducted at Screening and at the EOS/ET Visit. Physical examination evaluations at other study visits will be at the discretion of the Investigator, but should, at a minimum, include an assessment of the lymph nodes, liver, and spleen. Height will be recorded at screening only. Weight will be recorded at each study drug dosing visit.
8. Temperature (oral, axillary, or tympanic), blood pressure, heart rate, and respiratory rate will be recorded at each time point. Vital signs will be monitored every 30 minutes (±5 minutes) during the course of the treatment administration and at end of infusion or more frequently as necessary.
9. Women of childbearing potential will have a serum pregnancy test during Screening and urine or serum pregnancy tests on Day 1 prior to randomisation, and all subsequent study drug dosing visits. A serum pregnancy test will be repeated at EOS/ET Visit. Additional pregnancy tests should be performed whenever pregnancy is suspected or at the discretion of the Investigator. All tests will be performed by the local laboratory according to local practice.
10. Clinical laboratory tests (haematology/coagulation/biochemistry/urinalysis) will be performed by local laboratories, prior to administration of study treatment.
11. If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or Investigator judgment.
12. Hepatitis B surface antigen, hepatitis B core antibody, HBV DNA (as applicable), HCV antibody, HCV RNA (as applicable), and human immunodeficiency virus to be conducted by local laboratory. HBV DNA at Screening, Week 12 and all visits from Week 12 onwards (only for subjects with history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection). Additional monitoring/management of subjects who were HCV antibody positive (and HCV RNA negative) at Screening should be done in accordance with local practice and standard of care.

13. Tumour assessments for the purpose of assessing subject eligibility (with central imaging confirmation) and medical care will be performed by the investigational site at Screening, Weeks 12, 28, and 52 (EOS/ET Visit) by reviewing CT scans (Neck, chest, abdomen, and pelvis) with contrast. Computed tomography scans obtained up to 6 weeks prior to the first administration of study drug may be used for determining study eligibility provided they are of adequate quality for subsequent central review. Tumour assessments may also be performed on the CT component of positron emission tomography - computed tomography (PET-CT) scans with contrast if the quality of the CT part of PET-CT is equivalent to that of a standard CT. The same modality (CT or PET-CT) should be consistently used throughout the study evaluations. All imaging performed for the study will be forwarded to the central imaging vendor for review and assessment of response for the primary and other efficacy endpoints. Disease assessments are to be performed as scheduled according to Table 1–1, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays. Assessments are NOT to be scheduled based on the previous imaging time point, but rather Day 1 should be used as the Baseline when calculating when the on-study tumour assessments are to be performed (with consideration of visit windows).
14. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F] FDG-PET or PET-CT) scan will be obtained where available (according to study site standard of care) at Screening, Weeks 12, 28, and 52 (EOS/ET Visit). Positron emission tomography scans acquired up to 6 weeks prior to Day 1 may be used for screening provided they are of adequate quality for subsequent central imaging review.
15. Bone marrow biopsies or aspirations performed up to 12 weeks prior to the first administration of study drug may be used. Additional bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.
16. Before randomisation of the subject, all the Baseline assessments must be reviewed by the investigators for suitability of starting the study treatment.
17. The study drug proposed rituximab biosimilar [DRL_RI] or MabThera® will be administered as an i.v infusion, at a dose of 375 mg/m^2 of body surface area. Subjects will receive induction treatment consisting of a weekly i.v infusion for 4 weeks followed by maintenance treatment consisting of an i.v infusion every 8 weeks up to Week 36. Subjects will be pre-medicated before each infusion with acetaminophen, diphenhydramine, and 100 mg i.v methylprednisolone or their equivalent to decrease the incidence and severity of acute IRRs. Randomisation in IWRS and administration of first dose of study medication should take place on the same day and this will be considered as Day 1
18. **Only for the subjects identified for the PK and pharmacodynamic evaluation:** one PK sample will be taken prior to initiation of infusion (pre-dose or C_{trough}) and a second sample immediately prior to the end of the infusion on Days 1, 8, 15, 22, and Week 12.
19. **Only for the subjects identified for the PK and pharmacodynamic evaluation:** separate pharmacodynamic samples will be taken prior to initiation of infusion (pre-dose) and immediately prior to the end of the infusion on Day 1, prior to the initiation of infusion on Days 8, 15, 22, and at Weeks 12, 20, 28, and 36. Samples will also be collected at the Week 44 and 52 visits.
20. Samples for detection of BAb and NAb will be collected before the administration of study drug infusion on Day 1 and Day 22. Additional samples for detection of BAb and NAb will be collected prior to study drug infusion at Weeks 8 and 28, as well as at the visits of Week 44 and Week 52 (EOS/ET Visit).
21. COVID-19 testing (RT-PCR, Rapid Antigen test or test with similar nature antigen test but no antibody test) to be performed as close as possible but no more than 4 days before first dose administration. COVID-19 testing may be repeated at the discretion of the Investigator. Subjects should be randomised only after negative COVID-19 test result.

2 Introduction

Rituximab is approved for use in B-cell non-Hodgkin's Lymphoma (NHL), chronic lymphocytic leukaemia, rheumatoid arthritis (RA) in combination with methotrexate in adults with moderately-to severely-active RA who have inadequate response to one or more tumour necrosis factor antagonist therapies, and granulomatosis with polyangiitis and microscopic polyangiitis in combination with glucocorticoids.[1,2] Rituxan® is the commercially available innovator reference product in the United States (US); MabThera® is the commercially available innovator reference product in the European Union (EU). In Japan the commercially available product is Rituxan®. The proposed rituximab biosimilar (hereafter referred to as DRL_RI) is being developed as a potential biosimilar to Rituxan® and MabThera®. Rituximab, the innovator reference product approved in the EU (MabThera®) will be used as the selected reference medicinal product (RMP) for all study sites participating in this protocol.

The term "biosimilar" refers to a biologic drug that is developed to be similar to an existing approved RMP. Biosimilars are intended to treat the same diseases as the RMP using the same dose and treatment regimen. Unlike generic versions of chemically-synthesised small molecule therapies, biosimilars are not structurally identical to their RMP. This is due to the purity, characteristics, and activity of a specific product being dependent on, and sensitive to changes in the process by which it was manufactured. Therefore, the aim is to create a product with no clinically meaningful differences between the proposed biosimilar and the RMP in terms of pharmacokinetics (PK), safety, immunogenicity, and efficacy.

The demonstration of similarity in efficacy between a proposed biosimilar and the RMP is an essential component of a clinical study program that collectively provides the evidence of biosimilarity. The objective of the current study is to demonstrate equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen cluster of differentiation (CD)-20 positive, low tumour burden follicular lymphoma (LTB-FL) in the first-line treatment setting, as measured by overall response rate (ORR).

2.1 Study Rationale

The evaluation of PK, efficacy, and safety (including immunogenicity assessment) between a proposed biosimilar and the RMP is an essential component of an efficient clinical study program collectively providing the evidence of biosimilarity. Results from a previous study (Study RI-01-003) show that the 91% confidence interval (CI) for the test to- reference ratios of all pre-specified primary and secondary PK endpoints were within the pre-specified window of 80.00% to 125.00% for the comparisons of DRL_RI to -MabThera® and Rituxan®, and for the comparison of MabThera® to Rituxan®, demonstrating the PK similarity of the 3 products (Section 2.2.4.2).

The primary objective of the current study is to demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with CD20-positive, LTB-FL in the first line- treatment setting, as measured by ORR. While the use of rituximab monotherapy as first-line treatment of LTB-FL is not approved in the US or EU, it is frequently used [3,4,5] and has the potential to replace watch and wait as the treatment of choice for asymptomatic, LTB-FL.

2.2 Background

2.2.1 Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. It has an approximate molecular weight of 145 kilodaltons (kDa). Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.[1,2]

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 haematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissue. This antigen does not internalise 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.[2]

The fragment antigen-binding domain of rituximab binds to the CD20 antigen on B lymphocytes and the fragment crystallisable (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 C1q binding, and antibody dependent cellular cytotoxicity (ADCC) mediated by one 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.[2]

Rituximab is approved for use in NHL, chronic lymphocytic leukaemia, RA, and granulomatosis with polyangiitis and microscopic polyangiitis. Further information is contained within both the Prescribing Information of Rituxan® and public information including the Summary of Product Characteristics (SmPC) for MabThera®.[1,2]

2.2.2 Follicular Lymphoma

CD-20 positive, B-cell NHL is a heterogeneous group of malignancies with varying clinical outcomes.[6] The risk of mortality from NHL depends on whether it is indolent or aggressive; indolent forms of NHL, such as follicular lymphoma (FL), have significantly better prognosis than more aggressive forms like diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma.

Follicular lymphoma is the most common subtype of indolent NHL in the Western Hemisphere. With current therapy options, prognosis is favourable, with median overall survival (OS) exceeding 12 years. Recent advances in disease management and our understanding of the biology of FL have led to a dramatic change in the treatment landscape. Despite this progress, FL remains incurable with standard therapies.[7]

Tumour grade is used to classify FL based on the number of centroblasts per high-power field (HPF). In general, cases harbouring a greater number of centroblasts behave more aggressively and are associated with a higher risk of transformation to DLBCL. Grade 1 (<5 centroblasts/HPF) and Grade 2 (6 to 15 centroblasts/HPF) FL are combined in the World Health Organisation (WHO) classification given their similar clinical behaviour. Grade 3 FL can be further subdivided into 3a and 3b, with the latter distinguished by a lack of centrocytes. Despite a higher tumour grade, FL Grade 3a behaves like Grade 1-2 FL and as such should be approached in a similar fashion. FL Grade 3b represents a distinct entity characterised by a diffuse architectural pattern, frequent loss of CD10 expression, and absence of t (14;18) chromosomal translocation. Consequently, its clinical course and treatment mirror that of DLBCL.[7] Subjects with Ann Arbor Stage II, III or IV of histological Grade 1, 2, or 3a with at least one measurable lesion (Section 10.1.14), will be enrolled in this study.

2.2.3 Efficacy of Rituximab in Low Tumour Burden Follicular Lymphoma

Despite much study and debate, a major issue that remains for newly diagnosed patients with asymptomatic, LTB-FL is whether therapy is indicated. While all available randomised data fail to demonstrate a survival benefit with early therapy compared with a watchful waiting approach, the success and tolerability of rituximab has challenged this treatment paradigm leading to earlier treatment with rituximab monotherapy, with or without rituximab maintenance[8]. Rituximab has a favourable side effect profile compared to chemotherapy; therefore, a study was conducted to compare watch and wait to immediate treatment with rituximab in subjects with LTB-FL.[9]

Adult subjects with asymptomatic Stage II, III or IV FL (Grades 1 to 2 and 3a) were randomly assigned in a ratio of 1:1:1 to watch and wait (Arm A), rituximab 375 mg/m^2 of body surface area (BSA) weekly for 4 weeks (rituximab induction; Arm B) or rituximab 375 mg/m^2 of BSA weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years (from Month 3 to Month 25) (Arm C). The primary endpoints were time to initiation of new therapy (chemotherapy or radiotherapy) and effect on quality of life at Month 7 (i.e., 6 months after completion of rituximab induction).

A total of 463 subjects were randomised (187 Arm A, 84 Arm B, and 192 Arm C) with 95% of subjects having low tumour burden (LTB) according to predefined criteria similar to the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria. The other 5% had raised lactate dehydrogenase (LDH) but fulfilled the remaining GELF criteria. Radiological response was assessed at Months 7, 13, and 25.

There was a significant difference in the time to start of new treatment, with 46% (95% CI 39-53) of subjects in Arm A not needing treatment at 3 years compared with 88% (83-92) in Arm C (hazard ratio [HR] 0.21, 95% CI 0.14–0.31; p<0.0001). Seventy-eight percent (78%, 95% CI 69-87) of subjects in Arm B did not need treatment at 3 years, which was significantly more than in Arm A (HR 0.35, 95% CI 0.22–0.56; p<0.0001), but no different compared with Arm C (HR 0.75, 95% CI 0.41–1.34; p=0.33).

At Month 7, Arm A had an overall remission rate of 6%. Arm B had an ORR of 77%, with a complete response (CR) + unconfirmed complete response (CRu) of 47% and partial response (PR) of 30%. Arm C had a CR + CRu of 60% and a PR of 29% (ORR=88%). There were also differences observed in 3-year progression-free survival (PFS) between Arm B and the other 2 arms with the highest PFS rate in Arm C, followed by Arm B, then Arm A. A statistically significant treatment difference was observed for the comparison between Arm C and Arm B (HR 0.53 [95% CI 0.32-0.87; p=0.011], and for the comparison between Arm B and Arm A (HR 0.55 [95% CI 0.37-0.83; p=0.0034]). These data indicate that initial treatment with rituximab significantly delays the need for new therapy.[9]

Another study, RESORT, looked at the role of maintenance therapy in subjects with LTB-FL who received single agent rituximab.[10] Subjects received weekly doses of rituximab (375 mg/m^2 of BSA) for 4 weeks, and responders were randomised to maintenance rituximab (MR single- dose rituximab every 3 months) or rituximab retreatment (RR - rituximab weekly for 4 weeks at disease progression). The primary endpoint was time to treatment failure (TTF). A total of 384 subjects enrolled. Complete response or PR was achieved in 274 subjects (71%), who were then randomised to MR (n=140) or RR (n=134). The mean number of rituximab doses/subject (including the 4 induction doses) was 15.5 (range 5 to 31) for MR and 4 (range 4 to 16) for RR. With a median follow-up of 3.8 years, TTF was 3.9 years for MR versus 3.6 years for RR (p-value=0.8). At 12 months post randomisation, there was no discernible difference in health -related quality of life and anxiety between the 2 arms.

2.2.4 Dr. Reddy's Rituximab (DRL_RI)

Dr. Reddy's Laboratories (DRL) is developing a proposed biosimilar version of the chimeric anti-CD20 monoclonal antibody (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 kDa. Each of the heavy chains contains one 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 Rituxan® and MabThera® when compared by a battery of orthogonal analytical methods. The glycosylation variants (glycoforms) of DRL_RI are the same as those found in Rituxan® and MabThera®, and the proportions of each of the glycoforms are similar between the 3 proteins.

Further information can be found in the Investigators' Brochure (IB) for DRL_RI.[11]

2.2.4.1 Nonclinical Studies

2.2.4.1.1 *In Vitro* Pharmacology

The comparison of *in vitro* functional activities of DRL_RI, Rituxan® and MabThera® was performed using multiple cell-based and binding assays. Batches of DRL_RI, Rituxan® and MabThera® were compared using Two One-Sided t-Test analyses. A difference of 20% in the mean relative binding or potency was deemed acceptable. The CDC and the ADCC activities and the binding of DRL_RI, Rituxan® and MabThera® to CD20, C1q, FcγRI, FcγRIIa, FcγRIIb, FcγRIII, and FcRn were found to be similar. Therefore, DRL_RI, Rituxan® and MabThera® are considered similar in terms of their *in vitro* functional characteristics. [11]

2.2.4.2 Clinical Studies

The PK characteristics of DRL_RI, MabThera®, and Rituxan® were compared in a double -blind, randomised, 3 arm study CCI [redacted] conducted in subjects with moderate to severe RA. The results of the study showed that the 91% CI for the test to- reference ratios of all pre-specified primary and secondary PK endpoints were within the pre-specified window of 80.00% to 125.00% for the comparisons of DRL_RI to -MabThera® and Rituxan®, and for the comparison of MabThera® to Rituxan®, 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 drug infusions, AUC from start to 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 drug. 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. The results also showed that the safety and immunogenicity profiles and CD20positive -Bcell- depletions as well as the proportion of subjects meeting the American College of Rheumatology (ACR)20, ACR50, and ACR70 improvement criteria from Baseline to Week 24 and the mean change from Baseline to Week 24 in Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) were comparable across DRL_RI, MabThera®, and Rituxan®.[12]

2.3 Benefit/Risk Assessment

There is a substantial body of data related to the safety and efficacy of Rituxan®/MabThera® in subjects with B-cell NHL (Food and Drug Administration [FDA] Rituxan® prescribing information/European Medicines Agency [EMA] MabThera® SmPC).[1,2] A comprehensive head-to-head comparison of Dr. Reddy's rituximab antibody, DRL_RI, to the US-approved Rituxan®, and the European RMP (MabThera®) has demonstrated that DRL_RI is similar to Rituxan® and the RMP (Section 2.2.4.2). Thus, the risk/benefit of DRL_RI is expected to be comparable to that of Rituxan®/MabThera®.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of DRL_RI may be found in the IB for DRL_RI.[11]

3 Objectives and Endpoints

Objective	Endpoint
Primary	
To demonstrate the equivalent efficacy of DRL_RI and MabThera® in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by ORR up to Week 28, evaluated in accordance with published response criteria for malignant lymphoma.	The primary endpoint is BORR, defined as the proportion of subjects in each treatment group that achieve a best overall response of either CR, CRu or PR up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma. [13]
Secondary	
• To compare the ORR at Week 12 and Week 28, CR at Week 28, CR as a best response up to week 28, duration of response (DOR), PFS and OS of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL.	• Overall response rate at Week 12 and Week 28 based on central radiology review in accordance with published response criteria for malignant lymphoma[13]. • Complete Response (CR) rate at Month 7 (Week 28). • CR rate as a best response up to Month 7 (Week 28). • Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS. • Progression-free survival defined as the time from date of randomisation to the date of documented progressive disease (PD) or death due to any cause. • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/End of Study (EOS).
• To compare the safety, tolerability, and immunogenicity of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL.	• Adverse events, clinical laboratory values, vital signs, and electrocardiogram (ECG) • Anti-rituximab antibodies and their relationship with other outcome measures.

Objective	Endpoint
Exploratory	
• To compare ORR evaluated in accordance with the Lugano criteria [14] in subjects with CD20-positive, LTB-FL treated with either DRL_RI or MabThera®.	• Overall response rate based on the Lugano criteria [14] for those subjects with available positron emission tomography (PET) data.
• To explore the PK parameters of DRL_RI and MabThera®, using a population-PK modelling approach.	• Pharmacokinetic parameters (e.g., clearance and volume of distribution) for DRL_RI and MabThera® will be derived using a population-PK modelling approach.
• To explore the pharmacodynamic parameters of DRL_RI and MabThera®.	• Potential differences in pharmacodynamic parameters (e.g., area under the effect curve [AUEC] of circulating B-cells depletion) for DRL_RI and MabThera® will be investigated.

4 Study Design

4.1 Overall Design

4.1.1 Description

This is a Phase III, randomised, multicentre, double-blind, parallel-group study in subjects with previously untreated, Stage II-IV, CD20-positive, LTB-FL.

It is planned to randomise approximately 312 subjects (Please refer Section 9.2) at approximately ≥130 study sites worldwide.

The study will enrol subjects with CD20-positive, LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the GELF based criteria.[3,9]

Subjects will receive induction treatment consisting of a weekly i.v infusion for 4 weeks (375 mg/m^2 of BSA) followed by maintenance treatment consisting of an i.v infusion (375 mg/m^2 of BSA) every 8 weeks from Week 12 up to Week 36.[15]

Randomisation will be stratified by low-, medium-, and high-risk subjects using the CCI CCI CCI), as well as by tumour grade (1-2 Vs. 3a) and geographical area (USA, Europe and Asia-Pacific region).

Subjects will attend study visits every week (± 2 days) during the Induction Treatment Period (Weeks 1 to 4), at Week 8 (± 7 days), at Week 12 (± 7 days), thereafter every 8 weeks (± 7 days) up to Week 52 (EOS/Early Termination [ET] Visit). Study procedures include physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, tumour assessments, clinical laboratory tests, serum LDH and β-2 microglobulin, coronavirus disease 2019 (COVID-19) testing at screening and as deemed appropriate by the Investigator at any time during the study, AEs, concomitant medication, immunogenicity, and PK and pharmacodynamic samplings for the subjects in the corresponding subset.

All subjects completing the study (Week 52) will attend an EOS Visit. Subjects discontinuing the study before Week 52 for any reason will also attend an ET Visit. Subjects positive for hepatitis B at screening will be followed up to 24 months post last dose of rituximab in the study as outlined in Section 6.10.

Subjects with a prior history of hepatitis B infection or serological tests suggestive of previous hepatitis B infection will continue to receive hepatitis B virus (HBV) antiviral prophylaxis therapy for at least 12 months post last dose of rituximab in the study and will be monitored and reported

for reactivation for up to 24 months following completion of rituximab therapy as outlined in Section 6.10.

Subjects prematurely discontinued from treatment, but wishing to continue in the study, will return for an ET Visit 8 weeks after the last dose of study drug. The post-treatment discontinuation follow-up for subjects wishing to continue in the study is detailed below:

- If the reason for study discontinuation is disease progression, the subjects will be contacted by telephone for information on survival, AEs, and concomitant medications every 8 weeks, for a total observation period of 52 weeks.
- If the reason for study discontinuation is different from disease progression, subjects will continue to attend scheduled tumour assessments (at which AE and concomitant medication information will also be collected) up to disease progression or Week 52, whichever occurs first. If these subjects subsequently experience disease progression then they will continue to be followed up by telephone every 8 weeks from that point of identification and for a total observation period of 52 weeks, as described for subjects discontinued from study drug due to disease progression.

Clinical assessments will be performed before the start of each treatment cycle by the Investigator. Tumour assessments for the purpose of assessing subject eligibility and medical care will be performed by the investigational site at Screening and Weeks 12, 28, and 52 (EOS/ET Visit).

The primary endpoint is BORR, defined as the proportion of subjects in each treatment group that achieve a best overall response of either CR, CRu or PR up to Month 7 (Week 28, i.e., 6 months after completion of rituximab induction) based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] An exploratory analysis using the Lugano criteria[14] will also be performed as described in Section 3 and Section 9.4.1.3.

Sparse PK sampling will be performed in a subset of approximately 90 subjects (approximately 45 subjects per treatment group) (PK and pharmacodynamic subset) on Days 1, 8, 15, 22, and at Week 12 (approximately 45 subjects per treatment group, these subjects will be included after they provide written consent for these evaluations) to facilitate a population-based PK approach using nonlinear mixed-effects modelling. At each of these visits, one sample will be taken prior to initiation of infusion (pre-dose or trough plasma concentration [C_{trough}]) and a second sample will be taken immediately prior to the end of the infusion. Indicatively, C_{trough} should be obtained within one hour prior to the start of infusion (but not after it has been started) and the sample prior to the end of infusion within 10 minutes prior to the end of infusion. In all cases the sampling time should be accurately recorded (date and time with hour and minutes). Should it not be possible to collect

the sample in the specified time frame, the sample should be anyway collected and the sampling date and time accurately (to hour and minutes) recorded.

The sampling date and time also needs to be accurately recorded for the samples obtained within the window period.

Separate samples for the pharmacodynamic marker, peripheral blood B-cell count, will be obtained in the same subset of subjects sampled for PK. These will be collected on the same days as the PK samples, as well as at Week 20, 28, 36, 44, and 52 visits, to facilitate a descriptive pharmacodynamic evaluation using the AUEC of B-cell depletion, B-cell counts at selected time-points, and optional population PK / pharmacodynamic modelling.

Samples for the evaluation of anti-rituximab antibodies (anti-drug antibodies [ADA]), including binding antibodies (BAb) and neutralising antibodies (NAb) will be obtained before the administration of study drug on Days 1 and 22. Additional samples for detection of BAb and NAb will be collected prior to study drug infusion at Weeks 8 and 28, as well as at the visits of Week 44 and Week 52 (EOS/ET Visit). Analysis of BAb samples will follow a tiered approach of screening and confirmation. Samples that are confirmed positive for BAb will be further tested for titre and NAb determination using validated assays.

Safety endpoints are the incidence of reported AEs and changes in vital signs, clinical laboratory parameters and electrocardiogram (ECG) parameters.

4.1.2 Schedule of Assessments

An overview of the protocol visits and procedures is provided in Table 1–1. Refer to Section 8 for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may 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. Unscheduled visits (including reason) will be collected in the electronic case report forms (eCRF).

4.2 Discussion of Study Design

This study is designed to demonstrate the equivalence of DRL_RI to MabThera® in subjects with previously untreated, Stage II-IV, CD20-positive, LTB-FL, as measured by ORR.

The study will enrol subjects with LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the GELF based criteria.[9,16] CCI

CCI [9,10,17] CCI [13] CCI CCI [9,14]

During the study, subjects will attend study visits every week (±2 days) during the Induction Treatment Period (Weeks 1 to 4), at Week 8 (±7 days), at Week 12 (± 7 days), thereafter every 8 weeks (±7 days) up to Week 52 (EOS/ET Visit).

The dose of DRL_RI or MabThera® at 375 mg/m^2 of BSA will be administered as an i.v infusion.

4.3 Scientific Rationale for Study Design

This study uses a double-blind design in order to avoid subjective influences in the study conduct and results evaluation. Random assignment is used to ensure balancing of external influences between the study arms.

The subject population and endpoint (BORR) have been chosen to provide an appropriate sensitivity to eventual differences in efficacy and safety of the DRL_RI and the reference product. The LTB-FL setting allows treatment with rituximab as a single agent, which maximises the sensitivity to differences in efficacy and safety between DRL_RI and the reference product due to the lack of interference by the effects of the concomitant therapies. The use of BORR as an endpoint also maximises sensitivity to differences in a reasonable time in this population, where the time to tumour growth is prolonged.

The current standard of care in advanced FL is rituximab in combination with chemotherapy. The indication for this study, anatomically defined, LTB, CD-20 positive FL, is a slow growing malignancy and rituximab monotherapy is an acceptable treatment option according to various treatment guidelines.[3,4] The goal of treatment with rituximab monotherapy in LTB-FL is to relieve disease symptoms, to delay the time to treatments more difficult to tolerate such as chemotherapy, and to relieve anxiety related to disease.

Low tumour burden will be assessed according to the GELF based criteria.[9,16]A serum LDH level within normal limits will be required for enrolment as LDH is an important prognostic factor in FL.

4.4 Justification for Dose

The 375 mg/m^2 of BSA is the dose of the RMP in clinical use for the treatment of follicular lymphoma. Thus, the same dose is maintained in order to allow a comparative evaluation of DRL_RI safety and efficacy with those of the reference product at the doses in current clinical use.

4.5 End of Study Definition

Subjects who complete the study or subjects who discontinue from the study early will attend an EOS/ET Visit. Subjects experiencing disease progression will discontinue study drug and attend the ET Visit, which is to be scheduled 8 weeks after the last dose of study drug administration. These subjects will then be contacted by telephone for information on survival, AEs, and concomitant medications (Section 4.5.1) every 8 weeks, for a total observation period of 52 weeks (Section 4.5.1). Subjects discontinued from study drug due to a reason other than disease progression will also attend the ET Visit scheduled 8 weeks after the last dose of study drug, and then will continue to attend scheduled tumour assessments (at which AE and concomitant medication information will also be collected) up to disease progression or Week 52, whichever occurs first, as described in Section 4.1.1.

End of Study/Early Termination assessments are as follows:

1. Clinical assessments will include the following: Physical examination (including weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
2. Serum pregnancy test (human chorionic gonadotropin [hCG]) for women of childbearing potential. Female subjects with documented history of hysterectomy, bilateral oophorectomy, medically confirmed ovarian failure, or screening follicle stimulating hormone (FSH) test demonstrating post-menopausal status are exempted from pregnancy testing.
3. ECOG performance status assessments.
4. Clinical laboratory tests: Blood and urine samples will be taken for haematology, coagulation, biochemistry, and urinalysis.
5. Serum LDH and β-2 microglobulin evaluation.
6. 12-lead ECG (local ECG equipment with ECG to be read locally by a medically qualified and experienced ECG reader at the study site).
7. Viral disease screening at the EOS Visit.
8. Tumour assessments (using a computed tomography [CT] scan and, where available according to study site standard of care, a fluorine-18-fluorodeoxyglucose positron emission tomography [[^{18}F] FDG-PET] or PET-CT scan) based on central radiology review in accordance with the response criteria for malignant lymphoma.[13]
9. Samples for BAb and NAb will be obtained.

10. A pharmacodynamic sample will be obtained only in the subjects undergoing PK and pharmacodynamic assessments.
11. Bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.
12. Assess AEs.
13. Review concomitant medications.
14. COVID-19 questionnaire.

4.5.1 Telephone Assessments for Survival Follow-up

The procedures will include the following:

1. Check survival status.
2. Record AEs and concomitant medications.

4.5.2 Early Termination of Study

This study may be terminated prematurely at any time by DRL for medical, operational or ethical reasons at individual or all study sites.

If the study is prematurely terminated or discontinued, the Sponsor/designee will promptly notify the Investigator, institutions and all competent regulatory authorities in writing outlining the reasons for the termination. The Investigator or Sponsor/designee 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.

As directed by the Sponsor/designee, all study materials, except documents needed for archiving requirements, will be collected and all eCRFs completed to the greatest extent possible. 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.

4.5.3 Definition of End of Study and Primary Completion Date

End of Study is defined as the time at which all subjects enrolled in the study have been followed for 52 weeks unless lost to follow-up or the subject has died. The EOS is achieved at last subject last visit and when data from those visits have been reviewed by the Investigator or designee.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. For the purposes of analysis, the study will be unblinded to specified Sponsor/designee members (but not investigators or subjects) once all subjects have reached the primary endpoint through the end of Week 28 (or earlier termination of study drug), and the database is locked.

For all those persons who will have access to the interim analysis unblinded data and results, will sign a confidentiality agreement in order to maintain study blind until the general unblinding happens after the final database lock.

5 Study Population

5.1 Inclusion Criteria

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

1. Signed written informed consent.
2. Male or female subjects aged ≥18 years of age.
3. Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF based criteria. Subjects must have sufficient tissue samples available for the central pathology review (Section 8.1.1), and a centrally -confirmed diagnosis prior to being randomised. Should a subject be eligible as per the central imaging review but not as per the Study Centre Review the subject will be considered eligible if confirmed both by the Investigator and the Medical Monitor (MM). For any other disagreement in eligibility the subject will be considered ineligible.
4. Ann Arbor Stage II to IV (Section 10.1.14).
5. ECOG status of 0 to 1.
6. Low tumour burden follicular lymphoma defined as:
    - As per central radiological assessment, nodal or extranodal mass involvement with diameter measuring <7 cm

- As per central radiological assessment, involvement of ≤3 nodal sites with diameter measuring >3 cm
- Absence of systemic symptoms or B-symptoms* (asymptomatic).

  *B-symptoms defined as weight loss >10% within last 6 months, recurrent or continuous night sweats, intermittent or continuous fever recorded as axillary or oral temperature >38°C for at least 3 days
- As per central radiological assessment, absence of splenomegaly (defined as spleen size higher than 16 cm by CT scan)
- Absence of risk of vital organ compression based on clinical finding
- Absence of leukemic phase (leukemic phase defined as a count >5,000/μL of circulating tumour cells)
- Absence of clinically significant cytopenias (defined as a platelet count of <100,000/μL, haemoglobin <10 g/dL, or absolute neutrophil count <1,500/μL)
- Absence of clinically significant serous effusion based on clinical examination and CT scan
- Serum LDH not higher than the upper limit of normal (ULN) by local laboratory.

7. Subject has at least 1 measurable tumour mass in 2 dimensions as per central radiological assessment, and the mass must be:
   - Nodal lesion >15 mm in the longest dimension; or
   - Nodal lesion >10 mm to ≤15 mm in the longest dimension and >10 mm in the shortest dimension; or
   - Extranodal lesion with both long and short dimensions ≥10 mm.
8. Creatinine clearance ≥45 mL/min as calculated by Cockcroft-Gault method.
9. Aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) values ≤3 × ULN, total or conjugated bilirubin values ≤1.5 × ULN.
10. Life expectancy ≥3 months.
11. Able to comply with the study protocol.

12. If female subject, then subject should be non-pregnant, non-lactating. Adequate contraception or post-menopausal/non-childbearing status (e.g., women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history). Women of childbearing potential must practice effective birth control for the duration of the study and for 12 months after the last study drug dose. For this same duration, male subjects participating in the study should avoid passing the semen to female partners during sexual intercourse.

5.2 Exclusion Criteria

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

1. Prior use of rituximab or any CD20 mAb for any reason.
2. Any contraindication to the use of rituximab.
3. Any prior therapy for FL (including but not limited to chemotherapy, radiotherapy).
4. Subjects who, in the opinion of the Investigator, require additional concomitant treatment for lymphoma.
5. Evidence of histologic transformation to high grade lymphoma or DLBCL.
6. Known Central Nervous System (CNS) involvement by lymphoma. (Note: CNS imaging not required unless clinically indicated).
7. Subjects on chronic supra-substitutive doses (defined as doses in excess of 7.5 mg per day of prednisone or prednisone equivalent for a period longer than 3 weeks) of systemic glucocorticoids.
8. Prior malignancy (including recurrence) within 5 years of screening, other than non-melanoma skin cancer or intraepithelial cervical neoplasia, which should have been successfully treated more than 1 year before study inclusion.
9. Subjects with any of the following: known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV).
10. Subjects with positive serological test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C virus (HCV) antibody can only be included in the study if any of the following is fulfilled.[18,19]

a. Subjects with a negative HBsAg and positive total HBcAb must have a HBV deoxyribonucleic acid (DNA) level <20 IU/mL (or 112 copies/mL) by polymerase chain reaction (PCR) to participate in the study. In addition, it is required for these subjects to follow consultation with a Hepatologist / relevant expert regarding initiation, monitoring, and use of HBV antiviral therapy and the subject must be willing to undergo PCR HBV DNA testing during treatment and agree to receive treatment as indicated. HBV DNA re-test will be performed as per the schedule of assessments (see Table 1–1) and further as needed, at the discretion of the Investigator.

b. Subjects with a positive test because of HBV vaccination may be included (i.e., HBsAg negative, anti-HBs+, HBcAb–).

c. Subjects positive for HCV antibody are eligible only if the PCR test for HCV ribonucleic acid (RNA) is negative.

11. 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 drug (Day 1). If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.

12. Subjects who have received a live vaccine within last 3 months or non-live vaccine within 4 weeks of the first administration of study drug. *[Note: A need may arise for trial subjects to receive vaccine against COVID-19 while being a part of the study. All such decisions will be taken at the discretion of the Investigator in consultation with the CRO / Sponsor after due consideration to subjects' safety, national health policy of the respective country and overall need by the subject for such vaccine during the time of study participation]*..

13. Subjects with an active uncontrolled infection requiring systemic treatment at Screening or history of documented recurrent clinically significant infection within 6 months of study inclusion (e.g., 2 or more viral, bacterial or fungal infections requiring in-patient treatment).

14. Subjects with New York Heart Association (NYHA) class III or IV congestive heart failure or relevant arrhythmia or angina based on ECG with clinical judgment.

15. Subjects with known hypersensitivity to rituximab or its excipients, or to proteins of murine or other foreign origin.

16. History or presence of a medical condition or disease that in the Investigator's opinion would place the subject at an unacceptable risk for study participation.

17. Participation in any clinical study or having taken any investigational therapy during the 2-month period immediately preceding administration of the first dose of study drug.

18. Lactating or pregnant female.
19. Women of childbearing potential who do not consent to use highly effective methods of birth control (e.g., sterilisation, or other non-hormonal forms of contraception) during treatment and for at least 12 months after the last administration of study drug. True abstinence periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.
20. Subject has been previously randomised in this study.
21. Subject likely not to be available to complete all protocol required study visits or procedures.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study drug/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (reason[s] for the screening failure), eligibility criteria, and any serious adverse events (SAEs).

Individuals 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 MM. 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 as per local Guidance.

6 Study Intervention

6.1 Identity of Study Treatments

DRL_RI or MabThera® will be provided as study medication to the participating study sites.

6.2 Study Drugs Administered

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

A computer-generated randomisation schedule will be used to assign subjects to the treatment groups. Subjects will be assigned a subject number in the order of their acceptance into the study. This identifying number will be retained throughout the study.

Following signing of informed consent, subjects will be registered into the study using an interactive web response system (IWRS) to receive a unique subject identification number. Randomisation will be performed using IWRS. Subjects will be randomised in a 1:1 ratio to one of the 2 study treatment arms taking into account stratification by low-, medium-, and high-risk subjects using the CCI index (CCI), tumour grade (1-2 Vs. 3a; i.e., subjects with Grade 1 tumours should be pooled with those with Grade 2 tumours, resulting in 2 levels for this factor), and geographical area (USA, Europe and Asia-Pacific region):

- Arm A: DRL_RI
- Arm B: MabThera®

The study drug DRL_RI or MabThera® will be administered as an intravenous (i.v) infusion, at a dose of 375 mg/m^2 of BSA.

Subject BSA will be calculated using an accepted formula. The Mosteller, Du Bois, and Haycock formulae are considered acceptable. The same formula should be used for the calculation of all doses administered to the same subject.

Mosteller formula[20]:
BSA(m^2) = √([Height{cm} x Weight {kg}]/3600)

Du Bois formula[21]:
BSA(m^2) = 0.007184 x Height (cm)$^{0.725}$ x Weight (kg)$^{0.425}$

Haycock formula[22]:
BSA(m^2) = Weight (kg)$^{0.5378}$ x Height (cm)$^{0.3964}$ x 0.024265

Subjects will receive induction treatment consisting of 4 weekly i.v infusions followed by maintenance treatment consisting of an i.v infusion every 8 weeks up to Week 36. Subjects will be pre-medicated before each infusion with an anti-pyretic and an antihistamine (e.g., paracetamol [acetaminophen] and diphenhydramine), and 100 mg i.v methylprednisolone or their equivalent to decrease the incidence and severity of acute IRRs.

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 every 30 minutes, to a maximum of 400 mg/hour.

Subsequent Infusions: 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.

Infusions should be administered under close medical supervision. The infusion should be interrupted, or the infusion rate slowed for infusion reactions. If symptoms improve the infusion rate can be continued at one-half the previous rate.

The schedule of dosing is presented in Section 1.2.

6.2.1 Study Drug Infusion Preparation

Study drug (DRL_RI or MabThera®) solutions for infusion will be prepared by an unblinded pharmacist/authorised designee/unblinded qualified physician in this study. Unblinded pharmacist/authorised designee/unblinded qualified physician should use aseptic techniques appropriate to parenteral administration products.

Study drug will be administered by i.v infusion by blinded study personnel. Study drug vials and prepared solutions should be inspected visually for particulate matter and discoloration prior to administration. Do not use vials if particulates or discoloration are present.

6.2.2 Pre-Medication for Study Drug Infusions

All subjects should receive pre-medication with 100 mg i.v methylprednisolone or their equivalent to be completed at least 30 minutes prior to rituximab infusions to decrease the incidence rate and severity of acute IRRs. Pre-medication consisting of an anti-pyretic and an antihistamine (e.g., paracetamol [acetaminophen] and diphenhydramine), should always be administered before each infusion of rituximab.

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

6.2.3 Study Drug Administration

Study drug (DRL_RI or MabThera®) will be administered by i.v infusion using the escalating infusion rate in accordance with the EMA approved labelling for MabThera®. The infusion rate must be well controlled to reduce the incidence of serious IRRs.

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

The study drug infusion must be administered in the presence of the Investigator/medically qualified study site staff (to enable compliance), and in an environment where full resuscitation facilities are immediately available. Vital signs will be monitored every 30 minutes during the course of the treatment administration and at the end of infusion or more frequently as necessary.

The study drug will be administered at a dose of 375 mg/m^2 of BSA. Subjects will receive induction treatment consisting of weekly i.v infusions for 4 weeks, followed by maintenance treatment consisting of an i.v infusion every 8 weeks from Week 12 up to Week 36.

The instructions below should be followed in conjunction with the local product labelling if it differs from these instructions. An electronic infusion pump is required to be used.

- 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 every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent Infusions: 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 for the onset of cytokine release syndrome. Subjects who develop evidence of severe reactions, especially severe dyspnoea, 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 relating to the infusion reaction. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse 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.

Medication errors may result in this study from the administration of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength.

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

- Medication errors involving subject exposure to the study drug;
- 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, medication error should be captured on the medication error section of the AE page and, if applicable, any associated AE(s) captured on an AE eCRF page. All medication errors should be reported to the Sponsor's designated safety services and MM within 24 hours of awareness as described in Section 8.4.2. Expedited reporting of medication error/infusion error to regulatory authorities will be based on the local regulatory requirements.

Whenever the infusion is interrupted, the stop time and restart time should be recorded (with date, hour and minutes) along with initial start and final end time. Rates of infusion throughout should be recorded.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Packaging

DRL_RI and MabThera® will be supplied as sterile, preservative-free, non-pyrogenic, single-use vials CCI [redacted].

Each vial of DRL_RI will contain 100 mg unit dose of DRL_RI in 10 mL single-use vial or 500 mg unit dose of DRL_RI in 50 mL single-use vial.

Each vial of MabThera® will contain 100 mg unit dose of MabThera® in 10 mL single-use vial or 500 mg unit dose of MabThera® in 50 mL single-use vial.

These rituximab concentrates for solution for infusion will be supplied packaged as blinded supplies in the external packaging (carton) for all products identified with a unique container number. The external packaging (carton) of DRL_RI 100 mg/10 mL and MabThera® 100 mg/10 mL will appear identical. Similarly, the external packaging (carton) of DRL_RI 500 mg/50 mL and MabThera® 500 mg/50 mL will appear identical.

Each blinded carton will contain 1 vial of study medication, either DRL_RI 100 mg/10 mL or MabThera® 100 mg/10 mL for the 10 mL vial size, or either DRL_RI 500 mg/50 mL or

MabThera® 500 mg/50 mL for the 50 mL vial size. Each carton will be packaged with a tamper-resistant seal. The Sponsor/designee must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used.

6.3.2 Labelling

Medication labels will comply with the legal requirements of each country and be printed in the local language (where applicable). They will not disclose the unblinded study drug information.

6.3.3 Storage

All drug supplies for this study must be stored according to labelled storage conditions (2ºC to 8ºC). The Investigator, or an approved representative (e.g., unblinded pharmacist), will ensure that all study drug is stored in a secured (locked) area with restricted access, and in accordance with applicable regulatory requirements.

Drug should be stored in accordance with the drug label. Investigators and study site staff are reminded to check and record minimum and maximum temperatures daily (i.e., manually or by using alarm systems to alert of any excursions) and ensure that refrigerators and thermometers (periodically validated) and are working correctly as required for proper storage of study drugs. Any temperature excursions should be reported to the Sponsor/designee immediately.

The study drugs must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor/designee immediately. Once a deviation is identified, the study drug must be quarantined and not used until the Sponsor/designee provides documentation of permission to use the study drug.

6.4 Measures to Minimise Bias: Randomisation and 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.

After written informed consent is obtained from an eligible subject, a unique subject number will be assigned to this subject. This number will be created and allocated by the IWRS, when the subject first enters the system at Screening.

The randomisation codes will be computer-generated and kept by a statistician independent from the project team. Randomisation will be stratified by low, medium, and high-risk subjects using CCI (CCI), as well as by tumour grade (1-2 Vs. 3a) and geographical area (USA, Europe and Asia-Pacific region).

Randomisation methods will be fully described in the Randomisation Plan specification document.

Subjects who are eligible for randomisation will be assigned a unique randomisation number at the Baseline (Day 0 to Day 1) Visit by IWRS. This randomisation number identifies which treatment will be allocated to the subject and will be used to identify randomised subjects during the study. Subjects who withdraw after randomisation are not to be replaced and their randomisation number will not be re-used.

Dispensing of study drug will be coordinated by IWRS. The system will assign study drug corresponding to the randomisation arm. Due to the study drug not being identical in appearance, methods to maintain the blind of the study drug during dispensing and administration will be employed.

6.4.1 Procedure for Unblinding

The study site Investigator and appropriate project team members will be authorised to access the emergency unblinding functionality within the IWRS. The system will require the user to confirm if it is medically necessary to break the randomisation code 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 drug 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 IWRS. If time allows, the Investigator may contact the Sponsor designee MM 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 unblinded 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 the end of the study. Once a randomisation code has been broken for a subject, he/she must be withdrawn from the study. The Investigator must inform the Sponsor designee MM in writing within 24 hours. An SAE form should be completed and reported in accordance with Section 8.4.2.

6.5 Study Intervention Compliance

Study drug will be administered under the supervision of the Investigator and study site personnel.

At investigational site all activities related to handling of study drugs till administration to a subject should be performed by unblinded pharmacist/authorised designee/unblinded qualified physician. This person should be assigned by the Principal Investigator of a site and be responsible for:

- receipt of study drugs,
- storage of study drugs,
- dispensing of study drugs,
- preparation of study drugs for infusion,
- accountability and reconciliation of study drugs,
- preparation of study drugs for destruction (used, expired, not fit to use, unused after last subject last treatment).

Unblinded pharmacist/authorised designee/unblinded qualified physician will provide study drug to other investigators at a site after its dilution (as required by applicable instruction) ready for administration by means of infusion system.

Nobody except unblinded pharmacist/authorised designee/unblinded qualified physician among site's staff should be in contact with vials of study drugs – that keeps blinded design of the study.

Unblinded pharmacist/authorised designee/unblinded qualified physician may not be in direct contact (may not treat/administer study drug) subjects enrolled in the study.

It is expected that at each investigational site there should be 2 unblinded pharmacist/authorised designee/unblinded qualified physician – to ensure appropriate handling of study drugs while absence of one of the unblinded person (e.g., due to vacation).

Compliance will be monitored by study personnel at the study site by using the source documents and the eCRFs. The unblinded pharmacist/authorised designee/unblinded qualified physician responsible for drug preparation will keep accurate and complete dispensing and accountability forms showing the receipt and dispensation of the study drug.

6.6 Study Treatment Accountability

Records will be maintained of the delivery of study drugs to the study centres, the inventory at the study centres, the use of each subject and the return to the Sponsor/designee.

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 drug specified by the IWRS and that all study medication received from the Sponsor/designee is reconciled.

6.7 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 screening are regarded as **prior medication** and must be documented as such in the eCRF.

All medications still being taken by a subject at the time of signing the Informed Consent Form (ICF) and which continue to be taken during the study, as well as all medications started after signing of the ICF, are regarded as **concomitant medication** and must be documented as such in the eCRF. The use of concomitant therapy, including prescription and non-prescription drugs, non-drug therapy, and dietary supplements and herbal preparations, is permitted as appropriate to treat AE or co-morbid conditions. Concomitant administration of any other experimental drug or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy is prohibited during study participation. This includes administration of rituximab not included in the protocol scheduled treatment. If a subject requires tumour targeting treatment for FL other than the protocol-defined treatment with rituximab monotherapy, including, but not restricted to, other immunotherapies, chemotherapy, and radiotherapy, this will be defined as disease progression. The date the concomitant treatment was initiated will be collected in the eCRF.

Any other medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The MM should be contacted if there are any questions regarding concomitant or prior therapy.

During their participation in the study, subjects should not take any prescription or non-prescription drug without the permission of the Study Investigator. However, the permission of the Study Investigator should be waived for medical emergencies.

6.8 Dose Modification or Delays

Dose modification is not allowed in the study. All subjects will receive the recommended dose of 375 mg/m^2 of BSA.

During the Induction Treatment Period, window period of ± 2 days from scheduled date of dosing will be allowed. The subsequent cycles would be administered so as to maintain a 7-day cycle, thus ensuring the 7-day gap between these dose administrations.

During the Maintenance Treatment Period, window period of ± 7 days from scheduled date of dosing will be allowed. The subsequent cycles would be administered so as to maintain the required gap between successive doses.

Any delays beyond what is mentioned above should be discussed in detail. If the out of window visit is on account of an adverse event or for safety related reasons, discussion with Medical Monitor (MM) is required, hence please contact your CRO MM under these circumstances. And if any social / other reasons lead to an out of window visit, then please document the reason for visit delay by adding a note/ short description in eCRF. Every out of window visit (irrespective of the reason) should be documented as a deviation.

6.9 Study Medication Access after the End of the Study

The study drug DRL_RI will not be available after the completion of the study. MabThera® can be procured from the market.

6.10 Guidance for Hepatitis B and Hepatitis C Seropositive Subjects

Subjects who show evidence of prior hepatitis B infection may participate in the study following consultation with a Hepatologist / relevant expert regarding monitoring and use of HBV antiviral therapy, and provided that subjects agree to receive and comply with HBV testing and hepatitis B prophylactic therapy as recommended by the Investigator, or treating Hepatologist, or relevant expert. HBV re-test will be performed as per schedule of assessment (see Table 1–1) and further at the discretion of the Investigator. [18,19]

Additional monitoring/management of subjects who had HCV antibody positive (and HCV RNA negative) at Screening should be done in accordance with local practice and standard of care.

Subjects will continue to receive HBV antiviral prophylaxis therapy for at least 12 months post last dose of rituximab in the study (i.e. 36 weeks, or earlier in case of ET), and will be monitored as recommended by hepatitis experts in accordance with local practice and guidelines. HBV reactivation will be monitored and reported for up to 24 months following completion of rituximab therapy. If any subject develops reactivation of HBV or any other significant infections while on rituximab, the Investigator should immediately discontinue study drug, consult with hepatitis experts, and institute appropriate treatment. For details and management of other infections, refer to the current marketed rituximab prescribing information. It will be the Investigator's responsibility to ensure compliance to the antiviral treatment, regular follow-up for monitoring (i.e. laboratory tests, clinical examination, AE evaluation) with the Hepatologist / relevant expert of hepatitis B seropositive subjects and reporting of any reactivation events to the Sponsor immediately during and post study follow-up period of 24 months post last dose of rituximab. The investigator has to periodically update to the Sponsor about all such follow-up visits, treatment compliance with antiviral and other medications, tests results, and hepatitis B reactivation for up to 24 months post last study dose of rituximab. Detailed procedure and the needed documentation to ensure compliance to post study follow-up and measures will be outlined in an amended study agreement between the Sponsor / Designee and the Investigator.

Post study period of 52 weeks, all safety related events to be reported directly to the Sponsor's e mail address: *pharmacovigilance@drreddys.com*.

7 Discontinuation of Study Intervention and Subject Discontinuation

7.1 Discontinuation of Study Intervention

If new clinically significant findings occur, the Investigator should recheck that the continuation of the study intervention is allowed by the study protocol and is in the best interest of the subject. If the new findings met a protocol requirement for withdrawing the study intervention or the Investigator considers that the risk-benefit ratio of continuing the study intervention for the individual subject is not any longer favourable, the study intervention should be discontinued.

Refer to the Schedule of Assessments for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Temporary discontinuations should only be done for legitimate medical reasons.

7.1.2 Rechallenge

Based on the best interest of the subject, treatment may be restarted at the recommended dose of 375 mg/m^2 of BSA.

7.2 Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor/designee for safety, behavioural, 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 or is lost to follow-up, every effort will be made to contact the subject. All attempts to contact the subject and information received during contact attempts 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 52) Visit, if applicable, and follow-up with the subject regarding any unresolved AEs. The Investigator or sub-investigator will be responsible for reporting subject withdrawal to the Sponsor/designee. Subjects who withdraw after randomisation are not to be replaced and their randomisation number will not be re-used. If these subjects subsequently experience disease progression, then they will continue to be followed up as described in Section 4.1.1.

If a subject withdraws from the study, and also withdraws consent for disclosure of future information, no additional data should be collected. The Sponsor/designee may retain and continue to use any data collected before such withdrawal of consent.

Subjects shall be withdrawn during the course of the study when subject well-being is at risk, including but not limited to:

- Unacceptable AE.
- Subject is confirmed to be pregnant.

Subjects who experience disease progression in accordance with published response criteria for malignant lymphoma [13] (per Investigator assessment) are expected to be withdrawn from study drug, to attend the ET Visit, and to be followed up by telephone for survival as described in Section 4.1.1. Subjects who wish to remain in the study but withdraw from the study drug for any reason other than disease progression will return for an ET Visit and continue to attend scheduled tumour assessments up to disease progression or Week 52, whichever occurs first.

7.3 Loss of Subjects to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record/eCRF.
- Should the subject continue to be unreachable, he/she will be considered as have been lost to follow-up.

8 Study Assessments and Procedures

8.1 Study Assessments

For each study visit (except the Screening Visit) the subject will enter the study site in the morning and remain until approximately mid-afternoon. The designated study site personnel will take the appropriate blood samples from the subject, for various assessments, as indicated in the following sections. After the blood draws for the Baseline Visit (Day 0 to Day 1), subjects will receive the treatment i.v infusions in the presence of the designated study site personnel at each of the designated Induction Treatment Period (Weeks 1 to 4 [±2 days]) and Maintenance Treatment Period visits (Week 12 [±7 days], and every 8 weeks [±7 days] up to Week 36). Thereafter, subjects will continue to attend visits every 8 weeks (±7 days) in the Follow-up Period up to Week 52. A study physician will be available during treatment infusions to ensure subject safety in the event of an infusion-related reaction (IRR).

Computed tomography scans are required to determine subject care by the Investigator and allow central vendor assessment of the primary endpoint (BORR) using criteria as outlined in Section 3. For modern imaging equipment, where the CT component attached to a PET-CT scanner is equivalent to that of a standard CT, a PET-CT scan is also suitable for assessment of the primary endpoint. The CT portion for such a combined PET-CT scan should be of diagnostic quality as a standalone CT scan in terms of i.v contrast, noise and anatomical coverage across all visits. The same modality (CT or PET-CT) for an individual subject should be consistently used throughout the study evaluations. PET scans alongside conventional CT scans provide both an indication of pathological metabolic activity and precise anatomic location of tumour tissue, and are required to assess BORR using the more recent Lugano criteria.[14] Hence, where available as standard of care, all subjects should receive both PET and CT imaging to allow central vendor assessment of the primary and other efficacy endpoints.

8.1.1 Screening (Day -35 to -1)

Subjects will undergo a Screening Visit at least 0 days, but not more than 35 days prior to the planned first day of blinded study drug.

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 informed consent must be obtained from each subject prior to the conduct of any protocol-specific procedures.

Screening procedures and assessments will be as follows:

The assessments are suggested to be conducted in the following chronological order.

1. Completion of a COVID-19 related screening questionnaire.
2. Obtain Informed Consent using a written ICF from the subject in accordance with local regulations.
3. Register screening of the subject using the IWRS.
4. Review subject eligibility (inclusion and exclusion criteria) with central confirmation of histopathology.
5. Assessment of subject stratification status based on CCI criteria (CCI), tumour grade, and geographical area.
6. Histological confirmation of diagnosis (subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site). Subjects must have sufficient tissue samples available for the central pathology review (obtained on or within 12 months prior to the screening date), and a centrally-confirmed diagnosis prior to being randomised.
7. Document medical and oncology history.
8. Document subject demographics.
9. Clinical assessments will include the following: Physical examination (including a thorough assessment of the lymph nodes, liver, spleen, height and weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
10. Serum pregnancy test (hCG) for women of childbearing potential. Female subjects with documented history of hysterectomy, bilateral oophorectomy, medically confirmed ovarian failure, or screening FSH test demonstrating post-menopausal status are exempt from pregnancy testing.
11. ECOG performance status assessments.
12. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, and urinalysis.
13. Serum LDH and β-2 microglobulin evaluation.
14. TB screening (performed locally, if required by local regulation or practice).
15. Viral disease screening: HBsAg, HBcAb, HBV DNA (as applicable), HCV Ab, HCV RNA (as applicable), and HIV.

16. 12-lead ECG (local ECG equipment with ECG to be read locally by a medically qualified and experienced ECG reader at the study site).
17. Record prior and ongoing medications.
18. Tumour assessments based on central radiology review of images from a CT scan and, where available according to study site standard of care, a [^{18}F] FDG-PET or PET-CT scan. PET scans acquired up to 6 weeks prior to Day 1 may be used for screening provided they are of adequate quality for central imaging review.
19. Bone marrow biopsy (if no previous biopsy within the last 12 weeks before dosing is available). Procedures can be performed locally.

8.1.2 Treatment Period (Day 1 to Week 36)

Induction Treatment Period (Study Days 1, 8, 15, and 22 [Week 1 to Week 4 ± 2 days])

Subjects will attend study visits every week (±2 days) during the Induction Treatment Period at Weeks 1 to 4 ± 2 days.

Samples for the evaluation of ADA including BAb and NAb will be obtained on Days 1 and 22 before the start of the study drug infusion on the corresponding day.

Subjects will be pre-medicated before each infusion with acetaminophen, diphenhydramine, and 100 mg i.v methylprednisolone or their equivalent to decrease the incidence and severity of acute IRRs.

Baseline Visit (Day 0 to Day 1, prior to randomisation and administration of study drug)

Eligible subjects will return to the study site for the Baseline (Day 0 to Day 1) Visit. Subjects must satisfy inclusion/exclusion criteria in order to be eligible for randomisation. Before randomisation of the subject, all the baseline assessments must be reviewed by the investigators for suitability of starting study treatment.

Baseline procedures and assessments are suggested to be conducted in the following chronological order:

1. Completion of a COVID-19 related screening questionnaire.
2. COVID-19 testing (RT-PCR, Rapid Antigen test or test with similar nature antigen test but no antibody test) to be performed as close as possible but no more than 4 days before first dose administration. Thus, COVID-19 testing may also be performed during the last few days of the screening window, ensuring maximum time gap of 4 days between first dose of the study drug and COVID-19 testing.

3. Re-review subject eligibility (inclusion and exclusion) criteria based on the screening assessment to ensure that the subject continues to be eligible for inclusion into the study.
4. Clinical assessments will include the following: Physical examination (at discretion of the Investigator, but including weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
5. Urine or serum pregnancy test for women of childbearing potential (performed locally, according to local practice).
6. ECOG performance status.
7. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, and urinalysis.
8. Serum LDH and β-2 microglobulin evaluation.
9. Samples for immunogenicity assessments (BAb and NAb) prior to administration of study drug infusion.
10. Randomise the subject in accordance with the IWRS.
11. Randomisation in IWRS and administration of first dose of study medication should take place on the same day and this will be considered as Day 1.

Baseline Visit (Day 0 to Day 1, following randomisation)

Baseline procedures and assessments are suggested to be conducted in the following chronological order:

1. Pharmacokinetic samples will be taken; one sample prior to initiation of infusion (pre-dose or C_{trough}) and a second sample immediately prior to the end of the infusion (only in subjects undergoing PK and pharmacodynamic assessments).
2. A separate pharmacodynamic sample will be taken prior to initiation of infusion and a second sample immediately prior to the end of the infusion (only in subjects undergoing PK and pharmacodynamic assessments).
3. Study drug administration.
4. Assess AEs.
5. Record concomitant medications.

Study Days 8, 15 and 22 (Week 2 to Week 4 ± 2 days)

The procedures and assessments for the Induction Treatment Period are as follows:

1. Completion of a COVID-19 related screening questionnaire.
2. Clinical assessments will include the following: Physical examination (at discretion of the Investigator, but including weight), vital signs measurement (seated blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
3. ECOG performance status.
4. Urine or serum pregnancy test (performed locally, according to local practice).
5. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, and urinalysis.
6. Serum LDH and β-2 microglobulin evaluation.
7. Day 22 Only: Samples for BAb and NAb will be obtained before the infusion of study drug.
8. Pharmacokinetic samples will be taken; one sample prior to initiation of infusion (pre-dose or C_{trough}) and a second sample immediately prior to the end of the infusion on Days 8, 15, and 22 (only in subjects undergoing PK and pharmacodynamic assessments).
9. Separate pharmacodynamic samples will be taken prior to initiation of infusion (pre-dose, only in subjects undergoing PK and pharmacodynamic assessments) on Days 8, 15, and 22.
10. Study drug administration.
11. Assess AEs.
12. Review concomitant medications.

Week 8 ±7 days

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

1. Completion of a COVID-19 related screening questionnaire.
2. Clinical assessments will include the following: Physical examination (at the discretion of the Investigator), vital signs measurement (seated blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
3. ECOG performance status.
4. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, urinalysis, and pregnancy tests.

5. Serum LDH and β-2 microglobulin evaluation.
6. Samples for BAb and NAb will be obtained.
7. Assess AEs.
8. Review concomitant medications.

Maintenance Treatment Period (Week 12 to Week 36 ± 7 days)

Subjects will attend the study visit at Week 12 ± 7 days, and thereafter every 8 weeks (±7 days) until Week 36. The subjects will attend the study site preferably from the morning until approximately mid-afternoon.

The procedures and assessments for the Maintenance Treatment Period are as follows:

1. Completion of a COVID-19 related screening questionnaire.
2. Clinical assessments will include the following: Physical examination (at the discretion of the Investigator, but including weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
3. ECOG performance status assessments.
4. Urine or serum pregnancy test (performed locally, according to local practice).
5. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, and urinalysis.
6. At Week 28 Only: Samples for BAb and NAb will be obtained before the infusion of study drug.
7. Serum LDH and β-2 microglobulin evaluation.
8. Viral disease screening: HBV DNA (as applicable) and HCV RNA (as applicable).
9. At Week 12 and 28 only (Month 3 and Month 7, i.e. 2 and 6 months after completion of rituximab induction) tumour assessments (using a CT scan and, where available according to study site standard of care, a [^{18}F]FDG-PET or PET-CT scan) based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] Subjects who have withdrawn from study drug for any reason other than disease progression will also undergo tumour assessment at Week 28.

10. Bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.
11. Pharmacokinetic samples will be taken; one sample prior to initiation of infusion (pre-dose or C_{trough}) and a second sample immediately prior to the end of the infusion at Week 12 (only in subjects undergoing PK and pharmacodynamic assessments).
12. Separate pharmacodynamic samples will be taken prior to initiation of infusion (pre-dose, only subjects undergoing PK and pharmacodynamic assessments) at Weeks 12, 20, 28, and 36.
13. Study drug administration.
14. Assess AEs.
15. Review concomitant medications.

8.1.3 Follow-up Period (Week 44 to Week 52)

Week 44 ±7 days

The procedures and assessments for Week 44 are as follows:

1. Completion of a COVID-19 related screening questionnaire.
2. Clinical assessments will include the following: Physical examination (at the discretion of the Investigator), vital signs measurement (seated blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature).
3. ECOG performance status.
4. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, and urinalysis.
5. Serum LDH and β-2 microglobulin evaluation.
6. Samples for BAb and NAb will be obtained.
7. Viral disease screening: HBV DNA (as applicable) and HCV RNA (as applicable).
8. A pharmacodynamic sample will be obtained only in the subjects undergoing PK and pharmacodynamic assessments.
9. Assess AEs.
10. Review concomitant medications.

8.1.4 End of Study (Week 52 ± 7 Days)

The procedures and assessments for Week 52 (± 7 days) are as follows:

1. Completion of a COVID-19 related screening questionnaire.
2. Clinical assessments will include the following: Physical examination (at the discretion of the Investigator), vital signs measurement (seated blood pressure, heart rate, respiration rate, and oral, axillary, or tympanic body temperature) and 12 lead ECG.
3. ECOG performance status.
4. Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, urinalysis, and serum pregnancy tests.
5. Serum LDH and β-2 microglobulin evaluation.
6. Samples for BAb and NAb will be obtained.
7. A pharmacodynamic sample will be obtained only in the subjects undergoing PK and pharmacodynamic assessments.
8. Viral disease screening: HBV DNA (as applicable) and HCV RNA (as applicable).
9. Assess AEs.
10. Review concomitant medications.
11. At Week 52, tumour assessments (using a CT scan and, where available according to study site standard of care, a [^{18}F]FDG-PET or PET-CT scan): based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] Subjects who have withdrawn from study drug for any reason other than disease progression will also undergo tumour assessment at Week 52.
12. Bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.

8.2 Efficacy Assessments

The primary endpoint for efficacy is BORR, defined, as the proportion of subjects in each treatment group that achieve a best overall response of either CR, CRu or PR up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] This necessitates the use of bone marrow biopsies if bone marrow was involved at Screening or any abnormality occurred during treatment; combined PET-CT scans are not required

for this version of the response criteria, but are allowed if the CT portion has the slice thickness compatible with spiral CT scans.

Disease assessments are to be performed as scheduled according to Table 1–1, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays. Failure to perform any of the required disease assessments will result in the inability to determine disease status for the impacted time point. A series of incomplete disease assessments will result in inability to determine disease response status and censoring of PFS back to the time of the last full assessment that did not show progression. Frequently off-schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical study.

Assessments are NOT to be scheduled based on the previous imaging time point, but rather Day 1 should be used as the baseline when calculating when the on-study tumour assessments are to be performed (with consideration of visit windows). The CT scans should be performed with contrast agents, unless contraindicated for medical reasons. If i.v contrast is medically contraindicated, imaging without contrast can be used. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and magnetic resonance imaging should most often be used. Such cases will be reviewed by the medical team, and their inclusion in the Per Protocol (PP) Population will be discussed at the blinded data review meeting(s).

Investigators will review the screening PET-CT or CT scans to determine subject eligibility (eligibility should be confirmed based on central radiology review) for the study. Investigators will review the post-treatment PET-CT or CT scans to determine and provide appropriate medical care to subjects. All [^{18}F] FDG-PET and CT or PET-CT imaging data sets performed for the study will be transferred to a designated central imaging vendor to facilitate centralised quantitative response assessment of the primary and other efficacy endpoints. Details of the response assessment procedures are provided in the imaging charter.

8.3 Safety Assessments

The timing and frequency of safety assessments are described in Table 1–1.

Safety variables include the following:

8.3.1 Physical Examinations

A standard physical examination will be performed at every visit as indicated in Table 1–1. The following parameters and body systems will be examined and any abnormalities described: weight, height (at Screening), general appearance, skin (e.g., presence of rash), head, eyes, ears, nose, and

throat, lungs (auscultation), heart (e.g., auscultation for presence of murmurs, gallops, rubs), extremity exam for the presence of peripheral oedema, 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 drug should be recorded as AEs.

8.3.2 Vital Signs

Vital signs, including heart rate, blood pressure, respiratory rate, and oral, axillary or tympanic body temperature, will be measured as detailed in Table 1–1 and in the event of an infusion reaction.

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 5 minutes. The same arm and position should be used throughout the study, using an appropriate cuff size. All blood pressure readings should be measured after resting for at least 5 minutes. When the timing of these measurements coincides with blood collection, the blood pressure and heart rate should be obtained first.

Vital signs are to be obtained prior to each study drug 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's judgment.

8.3.3 Electrocardiograms

The 12-lead ECG measurement will be done under medical supervision at Screening and Week 52/EOS/ET. Before recording, subjects should be resting in a quiet supervised setting with minimal stimulation (e.g., no television, loud music, computer games) and lie in a resting position for 10 minutes before ECG recording.

Corrected QT interval (QTc) value (msec) will be calculated using the Fridericia formula, where:

$$QTc = \frac{QT}{\sqrt[3]{RR}}$$

with QT measured in msec 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 pre-existing condition or if a pre-existing condition worsens in frequency or intensity.

8.3.4 Clinical Safety Laboratory Assessments

Haematology, biochemistry, coagulation, and urinalysis will be conducted at Screening, on Weeks 1, 2, 3, 4, 8, 12, 20, 28, 36, 44, and 52. Serum pregnancy test will be conducted at Screening and EOS/ET. Urine or serum pregnancy tests will be conducted on Day 1 prior to randomisation, and all subsequent study drug dosing visits.

Blood and urine samples for haematology, biochemistry, coagulation, urinalysis and pregnancy tests should be sent to the local laboratory for analysis. Local laboratory normal ranges will be collected prior to first subject first visit at each study site (and in case, any change to reference range during course of trial) 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/designated site personnel.

The following parameters will be assessed:

- Haematology: red blood cell count, total haemoglobin, haematocrit, white blood cell count with differential counts (specific leukocyte populations to be reported as counts; percentages are optional), platelets count.
- Coagulation: prothrombin time.
- Biochemistry: β-2 microglobulin, albumin, ALP, ALT, AST, blood urea nitrogen, calcium, chloride, creatinine, creatinine clearance (Cockroft Gault formula), gamma-glutamyl transpeptidase, LDH, phosphate, potassium, random serum glucose, sodium, total bilirubin, total protein, and uric acid.
- Urinalysis (by dipstick or any other method): specific gravity, pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase or leukocytes, microscopic examination (if blood or protein is abnormal).

- Other screening tests: FSH (as needed in women of non-childbearing potential only e.g., women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history), serum β-hCG, pregnancy test (for women of childbearing potential), serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, and HCV antibody), HBV DNA (as applicable) and HCV RNA (as applicable). If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment, and COVID -19 testing (as applicable).

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

8.3.5 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be graded according to the definitions presented in Table 8–1.

Table 8–1 Eastern Cooperative Oncology Group Performance Status Definitions

Grade	Eastern Cooperative Oncology Group Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

8.3.6 Viral Disease Screening

Subjects will be tested for HIV, hepatitis B, and hepatitis C to determine eligibility.

HBsAg, HBcAb, HCV, and HIV are to be determined by each study site's local laboratory. Screening for HIV infection is to be performed only if not prohibited by local regulations.

8.3.7 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic and pharmacodynamic samples will be collected at time-points specified in Table 1–1. Pharmacokinetic and pharmacodynamic samples will be collected, processed and shipped as described in the central laboratory manual. All samples will be analysed by the designated analytical laboratory using a validated analytical method.

8.3.8 Immunogenicity Assessments

Blood samples for assessment of BAb and NAb will be collected at time-points specified in Table 1–1. BAb and NAb samples will be collected, processed and shipped as described in the central laboratory manual. All samples will be analysed by the designated analytical laboratory using a validated analytical method.

Analysis of BAb and NAb samples will follow a tiered approach of screening and confirmation. Samples that are confirmed positive for BAb will be further tested for titre and NAb determination using validated assays.

8.3.9 Histopathological Review of Diagnostic Tissue

To be eligible for this study, subjects must have tumour tissue available for review by a central pathology review committee. [redacted] CCI [redacted] The primary analysis for study outcome will be based on a centrally- confirmed- diagnosis documented at the time of randomisation.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

Adverse Event/Reaction

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

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study medication is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. Progression of the malignancy under study, including signs and symptoms progression, should not be reported as a serious adverse event. Hospitalisation due to signs and symptoms of disease progression should not be reported as serious adverse event. However, all AEs (including disease progression) fulfilling any of the seriousness criteria are reportable as SAE for the study subjects from sites in India.

Any relevant observations made at the Screening Visit (prior to signing the ICF) are to be recorded as a pre-existing condition; an AE will only be recorded if there is a worsening of the pre-existing condition during study conduct with regards to nature, severity, or frequency. An adverse drug reaction is an "untoward and unintended response to a study drug related to any dose administered".

All AEs judged by either the reporting Investigator or the Sponsor/designee as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression of "reasonable causal relationship" means to convey in general that there are facts or arguments meant to suggest a causal relationship.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, biochemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Serious Adverse Event

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

- Results in death.

  Death is not an AE itself, but an outcome. The cause of the death is the 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 a SAE that hypothetically might have caused death if it were more severe.

- Requires in-patient hospitalisation or prolongs existing hospitalisation (This does not include prolonged hospitalisation for study purposes)

  Hospitalisation is defined as at least one 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 hospitalisation due to pre-planned hospitalisations (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 hospitalisation due to unplanned complications. Following the initial discharge from hospital, subsequent hospitalisations are to be considered an SAE. "Social" hospitalisation, defined as administrative impossibility to discharge the subject is not necessarily an SAE. Complications that occur during hospitalisation 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. Hospitalisations 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 hospitalisation may be considered an SAE, when based on appropriate medical judgment, they may jeopardise the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment Emergent Adverse Event

Treatment emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose of study medication.

Infusion-Related Reactions

A pre-defined list of IRRs (using selected preferred terms from the Medical Dictionary for Regulatory Activities [MedDRA]) will be determined prior to unblinding. Details will be provided in the Statistical Analysis Plan (SAP).

8.4.2 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

Any relevant observations (including laboratory data) made at the Screening Visit (prior to signing the ICF) are to be recorded as a pre-existing condition on the medical history page of the eCRF. For [redacted] CCI [redacted] Those that were present both before and after signing the ICF should be recorded as medical history, and those with no past history should be considered as an AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, severity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome. A new AE must be recorded if the severity of the AE changes.

SAEs and AEs will be recorded starting after signing of informed consent until EOS Visit or in case of early termination until ET Visit or week 52, whichever occurs later (unless subject withdrew consent or lost to follow-up at or after ET). All SAEs and AEs have to be recorded, whether or not considered causally related to the study drug or to the study procedure(s).

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the eCRF. It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or Sponsor's designated safety services in lieu of completion of the AE/SAE in eCRF. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

In case the eCRF is down or unavailable due to technical difficulties at the site, the Investigator will use the back-up paper SAE form to report SAEs within 24 hours via fax or via email to the Sponsor's designated safety services. The paper SAE form and the contact details for reporting will be part of the site reference manual.

All ongoing AEs/SAEs should be followed up until resolution or stabilisation or the EOS/ET Visit, whichever occurs first, with the exception of any ongoing drug-related AEs/SAEs, which should be followed until the AE/SAE is stabilised, resolved, or, in the Investigator's opinion, the AE/SAE is unlikely to resolve due to the subject's underlying condition.

At any time after the EOS/ET Visit, if an Investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify the Sponsor/designee.

8.4.3 Assessment of Intensity

The Investigator will use the adjectives Mild, Moderate, Severe, Life-threatening, or Death to describe the maximum intensity of the AE. The US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 will be used to grade severity. [23]

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate: minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.

Severe: or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.

Life-threatening: urgent intervention indicated.

Death: related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 met one of the criteria for SAEs, listed in Section 8.4.1.

8.4.4 Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each 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. [redacted] CCI [redacted] 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 one 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:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

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, before reaching up to a decision on causality assessment:

- Time relationship between study drug intake and event's onset
- Dechallenge
- Rechallenge
- Medical History
- Study drug
- Mechanism of action of study drug

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

Action taken with study drug due to the AE:

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

Outcome:

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

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

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/PAREXEL 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). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

8.4.5 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study intervention, and unexpected (suspected unexpected serious adverse reaction [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 as per local regulations. These updates will include information on SUSARs and other relevant safety findings.

8.4.6 Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as an AE/SAE if any one 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 drug.

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.

8.4.7 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

8.4.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3).

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF within 24 hours of receipt of the information.

8.4.9 Regulatory Reporting Requirements for Serious Adverse Events

Investigators and other study site personnel must inform the Sponsor's designated safety services of any SAE that occurs (whether or not attributable to the study drug) in the course of the study within one day (i.e., immediately but no later than 24 hours or as per local regulation) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported to Sponsor's designated safety services by the Investigator within 24 hours or as per local regulation.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the Sponsor's designated safety services within 24 hours or as per local regulation as described above.

All SAEs and pregnancies will be recorded in the eCRF. As soon as the SAE/pregnancy is recorded in the eCRF, a notification alert will be sent to the Sponsor's designated safety services. A notification email of the event describing it in the e-mail text is not sufficient. Whenever required applicable local SAE reporting Form will be used (e.g., Appendix XI in India), in addition to eCRF update.

Source documents relevant for the SAE should only 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.

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 drug 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 eCRF SAE page accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements for SAEs.

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

The Sponsor/designee representative will work with the Investigator to compile all the necessary information and ensure that the appropriate Sponsor/designee representative receives a report within 24 hours for all SAEs.

The Sponsor/designee will bear responsibility of expedited and periodic reporting to the health authorities according to national requirements. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths and SUSARs) to the IEC/IRB that approved the study. [redacted]
CCI
[redacted]

8.4.10 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study drug 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 in the eCRF. Follow-up should be performed up to delivery, after the examination of the newborn, and until 12 weeks of age, when follow-up information regarding the pregnancy and the outcome of the newborn should be entered in the eCRF.

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's designated safety services via the eCRF.

Pregnancy outcomes must be collected for the female partners of any males who took study drug 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's designated safety services using the reporting details provided in Section 8.4.2 within 24 hours of awareness.

8.4.11 Death Events

Should a death occur within the study period or within 16 weeks after the last administration of study drug an AE form and an SAE 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 Sponsor's designated safety services within 24 hours as described in Section 8.4.2. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. However, death due to disease progression to be reported as SAE from sites in India.

8.5 Study Conduct During the COVID-19 Pandemic

COVID-19 is a viral illness caused by the novel coronavirus (also called SARS-CoV-2) and has impacted most of the countries across the globe. It was declared as a global public health emergency by the WHO on 30 Jan 2020, and was declared as a pandemic on 11 Mar 2020. This pandemic has impacted the conduct of clinical trials in various ways.

8.5.1 Contingency Measures Implemented During the COVID-19 Pandemic

In the current global outbreak of COVID-19, Dr. Reddy's Laboratories (DRL) has recognized the potential impact on the conduct of RI-01-006 study due to various reasons. Considering that the safety of study participant is paramount, DRL has initiated various contingency measures for the well-being of subjects and in order to ensure compliance with guidance issued by various regulatory agencies:[24,25]

- COVID-19 protective measures: Recommendation to study sites to inform and encourage all study subjects to practice COVID-19 basic protective measures at all times.
- COVID-19 testing and COVID-19 related screening questionnaire:

a. Each subject being randomized will undergo COVID-19 testing (preferably RT-PCR) and only subjects with confirmed negative test results will be administered the study drug. Additional testing for COVID-19 during the course of study may be performed at the discretion of the Investigator. All such test results will be documented appropriately in CRF.

b. COVID-19 related screening questionnaire to rule out active COVID-19 infection as well as to evaluate further if potential study subjects are at risk of acquiring COVID-19 at screening visit and during the study period. Study drug will be administered only in those subjects who are considered at no-risk by the Investigator based on this evaluation.

- Inform Consent Document (ICD) amended to include possible risks related to COVID-19 and rituximab treatment. All ongoing subjects will undergo re-consent with a newer version of the ICD, after approval from a respective ethics committee (EC). All new subjects being screened will be asked to give their consent using the newer version of the ICD.
- Advise study sites to prioritize subjects' safety and priority care in the event of COVID-19 infection.
- The Investigator must stop rituximab treatment if any of the study subjects acquire COVID-19 infection while in the study. Re-institution of therapy should be done after careful benefit risk assessment by the Investigator once the subject has been confirmed as cured of COVID-19 with appropriate laboratory testing.
- The Investigator is encouraged to do telephonic inquiry of study subjects to know about their overall well-being, adverse events, including suspected COVID-19 symptoms, concomitant medications etc.
- COVID-19 events in the study are to be considered as "Events of Special Interest (EOSI)" 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 as an SAE.

All details of remote monitoring, including discussion with sites on informed consent process, subject eligibility, review of central lab data, review of data entry, query resolution, pending actions, review of protocol deviations etc., have been captured in the monitoring plan, as applicable.

Detailed information about the type of data to be collected, handling of missing data or assessments/procedures 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 and additional safety contingency measures will be generated based on the available data, if required. Corresponding details will be mentioned in the SAP.

Based on the evolving COVID-19 pandemic, the Sponsor will revisit these contingency measures for any further changes, or for their continuation/discontinuation, as needed, while ensuring subject safety and trial data integrity throughout the conduct of the study.

8.6 Treatment of Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine in an amount that is higher than the protocol-specified dose. Rounding off is unavoidable in the preparation of rituximab infusion solutions. Due to this reason, excess CCI [redacted] CCI [redacted] for the subject will not be considered an overdose. Every overdose must be reported to the Sponsor's designated safety services within 24 hours of awareness as described in Section 8.4.2, irrespective of whether the overdose was associated with an AE/SAE. Subjects who experience overdose should be closely monitored.

9 Statistical Considerations

9.1 Statistical Hypotheses

9.1.1 General Principles

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 summarised 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.

CCI [redacted]

An additional analysis may be performed based on country specific requests/ requirements by the relevant authorities.

An SAP will be prepared and finalised before the study data are unblinded.

The statistical analysis will be performed using SAS® version 9.4 or higher.

9.1.2 Missing Data

Imputation of missing data in the primary efficacy analysis is described in Section 9.4.1.1 Partial dates for start or stop date of AEs will be imputed in an appropriately conservative way. Detailed methods for handling missing data will be given in the SAP. For substantial missing assessments due to the COVID-19 pandemic additional sensitivity analyses will be performed to determine if there was an impact on the efficacy endpoints. Methods for handling missing data should outline the assumptions utilized and discuss if this method of choice may have an effect on the estimate of the treatment effect.

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

9.1.3 Inter-current events due to COVID-19

Handling (i.e., analysis and presentation) of intercurrent events and data/visit impacted due to COVID-19 pandemic will be described in the SAP.

The following events are considered as intercurrent events due to COVID-19 pandemic and any study data missing as an outcome of these events will be handled as missing data impacted due to COVID-19:

- COVID-19 infection or death due to COVID-19 (as an Event of Special Interest)
- Protocol deviation including missing assessment due to COVID-19 pandemic
- Any other documented event which may interfere the study conduct and is reasonable related to COVID-19 pandemic

Full details of the COVID-19 related intercurrent events definitions will be provided in SAP.

9.1.4 Demographic and Baseline Characteristics

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

9.1.5 Subject Disposition

The following will be summarised (overall and by treatment group where applicable):

- Subjects screened
- Subjects randomised
- Subjects treated
- Subjects in each analysis population
- Subjects completing the study/withdrawing early (including withdrawal reason)
- Subject allocation by study site

9.2 Sample Size Determination

Published data for rituximab treatment versus a "watch and wait" strategy in the first line treatment of LTBFL (Ardeshna et al. 2014) revealed [redacted]
CCI
[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

Based on the observed pooled best overall response (BOR) rate, up to week 28, the revised total sample size obtained in the BSSR is 312 subjects (156 per group) to be recruited.

9.3 Populations for Analyses

9.3.1 Intent to Treat Population

The Intent to Treat (ITT) Population will include all randomised subjects. The primary efficacy analysis will be based on the ITT Population.

9.3.2 Per Protocol Population

The PP Population will include all subjects who are randomised into the study, receive at least one dose of study drug (sufficient compliance to be evaluated under blind conditions), have measurable disease at Baseline as confirmed by central review, have an at least one available valid response evaluation up to 7 months (± 4 weeks), and no major protocol deviations (such as administration of a forbidden treatment) that would significantly impact the primary efficacy endpoint. If the forbidden treatment was administered due to PD, the subject will be included in the PP Population as a non-responder. In the EMA analysis, both ITT and PP population will be considered as primary.

Subjects will be considered to have a valid response evaluation if all required tests in accordance with published response criteria[13] are available and have been obtained within ± 28 days of the scheduled date, and the central imaging reviewers consider all imaging at 3 months (Week 12) and 7 months (Week 28) as properly evaluable for size comparison with the baseline images, and subjects have not received forbidden medications or other treatments for LTB-FL.

Analysis of the PP Population may allow easier detection of any differences in treatment since the population includes only subjects who adhere to the protocol. Identification of the PP Population will be determined at one or several blinded data review meetings prior to unblinding.

9.3.3 Safety Population

The Safety Population will include all subjects who have received at least one dose of study drugs. The Safety Population will be used for safety analysis.

9.3.4 Pharmacokinetic Analysis Population

The PK Analysis Population will include all subjects in the PK and pharmacodynamic subset who have at least one available pre-dose sample and one quantifiable study drug concentration after initiation of treatment.

Subjects will be considered included in the PK and pharmacodynamic subset if they participate in the PK and pharmacodynamic evaluations, have provided their written consent to participation and randomised to the study within the PK and pharmacodynamic subset.

9.3.5 Pharmacodynamic Analysis Population

The Pharmacodynamic Analysis Population will include all subjects in the PK and pharmacodynamic subset and sampled for pharmacodynamics who have at least an available

pre -dose pharmacodynamic sample and an available pharmacodynamic sample obtained after the administration of the first dose of rituximab has started.

Subjects will be considered included in the PK and pharmacodynamic subset if they participate in the PK and pharmacodynamic evaluations, have provided their written consent to participation and randomised to the study within the PK and pharmacodynamic subset.

Subject evaluability for specific parameters will be decided under blinded conditions.

9.4 Statistical Analyses

The SAP will be developed and finalised prior to data base lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints. Further details are presented in the SAP.

9.4.1 Efficacy Analyses

9.4.1.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the BORR i.e., the proportion of responders in each treatment arm who achieve a best overall response of either CR, CRu or PR up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] Subjects who are included in the ITT Population but do not have efficacy assessments will be assessed as non-responders. The estimated difference (DRL_RI minus MabThera®) and its 95% CI will be obtained using the test -based exact binomial confidence interval method.[27, 28] Equivalence will be concluded for FDA if the 90% CI and for EMA if the 95% CI of the BORR difference is completely contained within the pre-defined interval (-17%, 17%). [redacted]
CCI [redacted]. Full details of the primary endpoint analysis including multiplicity considerations will be provided in the SAP.

Various sensitivity analyses will be conducted to confirm the robustness of the primary efficacy analysis result, including but not limited to:

- CCI [redacted]

- [redacted]
  CCI
  [redacted]
- [redacted]
  CCI
  [redacted]
- [redacted]
  CCI
  [redacted]

Additional details regarding sensitivity analyses for inter current events due to COVID-19 will be available in SAP.

9.4.1.2 Analysis of Secondary Efficacy Endpoint

Secondary efficacy endpoints include the following:

- Overall response rate at Week 12 and Week 28 based on central radiology review in accordance with the response criteria for malignant lymphoma[13].
- CR rate at Month 7 (Week 28).

- CR rate as a best response up to Month 7 (Week 28).
- Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS.
- Progression-free survival defined as the time from date of randomisation to the date of documented PD or death due to any cause.
- Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/EOS.

Time to event endpoints (PFS, OS, and DOR) will be summarised using Kaplan-Meier (K-M) survival curves. The K-M survival estimates, together with the number of subjects, percentage of subjects to experience the event, and the number and percentage of subjects censored will be summarised in a table by treatment group. The ORR at Week 12 and Week 28, CR at Month 7 (week 28) and CR rate as a best response up to Month 7 (Week 28), duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS, progression-free survival defined as the time from date of randomisation to the date of documented progressive disease (PD) or death due to any cause and overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/End of Study (EOS) will be summarised by treatment group using frequency and percentage (including the 95% CI).

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

9.4.1.3 Analysis of Exploratory Endpoint

The BORR will also be evaluated based on the Lugano criteria[14] for those subjects with available PET data and summarised by treatment group using frequency and percentage (including the 95% CI).

9.4.2 Safety Analyses

Safety will be reviewed throughout the study in a blinded manner by the study team.

The safety endpoints will include the following:

- Incidence of AEs, as assessed by the NCI CTCAE version 5.0.
- Incidence of infusion reactions in each treatment group, where IRRs will be pre-defined.
- Vital signs.

- Clinical laboratory parameters.
- 12-lead ECG.
- ECOG performance status.
- Physical examination.

TEAEs including Events of Special Interest (COVID-19 infection or death due to COVID-19 infection) will be described using descriptive statistics and coded according to the MedDRA (version 21.1 or latest) system organ class and MedDRA preferred term, graded according to CTCAE version 5.0, by treatment group and overall. TEAEs observed, based on the onset date, during the rituximab induction and maintenance will be summarised separately by treatment group. Drug-related TEAEs and SAEs, TEAEs leading to study discontinuation, and death will also be summarised by treatment group and overall.

Clinical safety laboratory data: clinical safety laboratory data will be presented by treatment group and overall. For each visit, the actual result and the change from baseline will be presented. Shift tables will be presented as appropriate.

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

The safety analysis will be based on the Safety Population and will be analysed according to the treatment they actually received. Detailed methods will be described in the SAP.

9.4.3 Subgroup Analysis

Subgroup analyses will be performed to examine efficacy and safety by CCI and other factors of interest. Detailed methods will be described in the SAP.

9.4.4 Pharmacokinetics Assessment

Using data from CCI, a population-PK model will be applied to the sparse PK data and potential differences in parameters such as clearance and volume of distribution for DRL_RI and RMP will be investigated using nonlinear mixed-effects modelling. Anti-drug antibodies status will be evaluated as a potential covariate in the population-PK model.

A separate analysis plan for the population-PK modelling will be developed and results will be provided in a separate population-PK report.

9.4.5 Pharmacodynamics Assessment

Peripheral blood B-cell counts will be comparatively evaluated for potential differences in parameters such as the area under the B-cell depletion-time curve (depletion AUEC).

Depletion is defined as Baseline (pre-dose at Visit 1) count minus the measured value.

The AUEC will be calculated using the linear trapezoidal rule. Only the values up to the last value below the individual subject baseline count will be included in the AUEC calculation.

Potential differences between DRL_RI and MabThera® in the AUEC will be investigated using a linear mixed-effects model with treatment as a fixed effect and subject as a random effect.

On the basis of B-cell counts a population pharmacodynamics evaluation including population pharmacokinetics-pharmacodynamics evaluation might be performed which will be evaluated in a separate analysis plan.

9.4.6 Immunogenicity Assessment

Immunogenicity data (BAb and NAb) will be summarised and analysed descriptively for each scheduled protocol assessment time point.

9.4.7 Reporting Timeframes

When all subjects have completed Week 28 (or the EOS/ET Visit for subjects discontinued prior to Week 28), the primary endpoint (BORR up to Week 28) will be analysed using centrally-reviewed radiology assessments and a study report produced. Available safety data and other secondary and exploratory endpoints may also be reported at that time including ORR at Week 12 and Week 28. An addendum study report will be provided to applicable regulatory authority when all subjects have completed the study, including updated safety data and secondary endpoints for time to event endpoints. Further details will be provided in the SAP.

Pharmacokinetic and pharmacodynamic endpoints will be reported as discussed in Section 9.4.4 and Section 9.4.5.

9.4.8 Other Analyses

Pharmacokinetic, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP. The population-PK analysis and pharmacodynamic analyses are presented in Section 9.4.4 and Section 9.4.5, respectively.

9.5 Interim Analyses

There will be no interim analysis.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IEC/IRB by the Investigator and reviewed and approved by the IEC/IRB before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
    - Notifying the IEC/IRB of SAE or other significant safety findings as required by IEC/IRB procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. [redacted]
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10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC/IRB or study centre.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.
- For subjects who are unable to read and write, the subject information sheet and ICF will 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 or legally acceptable representative 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.

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.

10.1.4 Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Site Manager (CSM) or Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

10.1.5 Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

- All data generated by the site personnel will be captured electronically at each study centre using eCRFs. Data from external sources (such as laboratory data) will be imported into the database or may be manually entered. Once the eCRF clinical data have been submitted to the central server at the independent data centre, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the eCRF. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.
- The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF.

10.1.5.1 Quality Assurance Audits

Study centres, the study database and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or CRO on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

10.1.5.2 Study Monitoring

The Sponsor has engaged the services of a CRO, to perform all monitoring functions within this clinical study. The CRO monitors will work in accordance with CROs' SOPs and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study centre, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study centre.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each study centre while subjects are enrolled in the study. The monitor will submit written reports after each monitoring visit to the clinical project manager/site visit report reviewer. On each occasion, contact with the Investigator will be made, regardless of whether it is by phone or in person. Telephone Contact Reports will be completed by monitors to document telephonic discussion with the sites.

The Investigator will allocate adequate time for monitoring activities by the CRO. The Investigator will also ensure that the study monitor, other designee, or Quality Assurance Reviewer is given access to all the study-related documents and study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and the study centre has adequate space to conduct the monitoring visit.

10.1.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established for the study, and operate according to procedures described in the DMC Charter. All meeting proceedings will be documented.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. It is essential that all samples are analysed at the laboratories specified for this study.
- The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports.
- The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

10.1.9 Publication Policy

The Sponsor shall retain the title and the right to publish all documentation, records, raw data, specimens or other work product generated pertaining to the study ("Data") conducted by the site (site includes the Investigator and the Institution). The site shall maintain confidentiality and not disclose or divulge such "Data" to any third party.

10.1.10 Protocol Approval and Amendment

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 must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study. In case of any changes implemented due to medical emergencies, the same needs to be promptly reported to the Sponsor and the IEC/IRB.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/IRB/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug (IND) 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.

10.1.11 Protocol Deviations

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 Ethics Committee's established procedures, will inform the Ethics Committee of protocol deviations.

All instances where the requirements of the study protocol are not complied with, will be captured in the eCRF and the study monitor will prepare 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 clinical study report.

10.1.12 Liability 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. The insurance will pay only when the Sponsor becomes legally obligated to compensate for the treatment; the Sponsor will cover the cost as per the local requirements. 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:

- A serious GCP or protocol deviation by the Investigator, Sub-Investigator, or Site Team (except deviation medically necessary to avoid an immediate hazard to the study subjects).
- Intentional act or negligence on the part of the Investigator, sub-investigator, or Site Team, or malpractice thereby.

- Injury caused by unlawful act or delinquency of a third party.
- Injury caused by intentional act or negligence of the subject.
- Hired person/Contracted person.

For studies conducted in the US and Europe, the policy does not cover:

- Bodily injury or property damage arising out of any human clinical study which has not been approved/placed on clinical hold/ordered to be discontinued by the governmental or regulatory authority having jurisdiction over the study (unapproved human clinical studies).
- Bodily injury or property damage arising out of any human clinical study for which the governmental or regulatory authority having jurisdiction over the study has withdrawn approval (unapproved human clinical studies).

For studies conducted in India and Rest of the World, (excluding non-admitted countries), coverage is on a legal liability basis depending on the local laws where the study is happening. Coverage will be for damages and or compensation or claimant's costs and expenses in respect of any claim made by the research subjects for bodily injury arising out of any study conducted by or on behalf of the Insured in connection with the business.

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

Any event/SAE is to be notified to the Sponsor or Sponsor's designee on a promptly and timely basis.

10.1.13 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration

to data protection and medical confidentiality. The Investigator assures PAREXEL and the Sponsor of the necessary support at all times.

10.1.14 Ann Arbor Staging - Cotswolds Recommendations

Table 10–1 Ann Arbor Staging

Stage	Description
I	Involvement of a single lymphatic region (I), or localised involvement of a single extralymphatic organ or site (IE).
II	Involvement of 2 or more lymphatic regions on the same side of the diaphragm (II); or localised involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE).
III	Involvement of 2 or more lymphatic regions on both sides of the diaphragm (III), which also may be accompanied either by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIIE, S).
IV	Diffuse or disseminated involvement of one or more extralymphatic organ or tissue, with or without associated lymph node involvement. Bone marrow or liver involvement will always be considered as Stage IV.

Data source:

Ann Arbor Staging: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31:1860-61.

Cotswolds Recommendations: Lister TA, Crowther D, Sutcliffe SB, et al. Staging for Hodgkin's disease. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989;7:1630-36 (Erratum; J Clin Oncol. 1990;8:1602)

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10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10-4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Haematology	Haematocrit	White blood cell with differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)[1]
	Platelet count	
	Red blood cell count	
	Total haemoglobin	
Coagulation	Prothrombin time	
Clinical Chemistry	β-2 microglobulin	Gamma-glutamyl transpeptidase
	Albumin	Lactate dehydrogenase
	Alkaline phosphatase	Phosphate
	Alanine aminotransferase	Potassium
	Aspartate aminotransferase	Random serum glucose
	Blood urea nitrogen	Sodium
	Calcium	Total bilirubin
	Chloride	Total protein
	Creatinine	Uric acid
	Creatinine clearance (Cockroft Gault formula)	
Routine urinalysis (by dipstick or any other method)	Specific gravity	Bilirubin
	pH	Urobilinogen
	Protein	Nitrite
	Glucose	leukocyte esterase or leukocytes
	Blood	Microscopic examination[2]
	Ketones	

Laboratory Assessments	Parameters	
Other Screening Tests	Follicle stimulating hormone (as needed in women of non-childbearing potential only e.g., women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history)	Serology (HIV antibody, HBsAg, hepatitis B core antibody, and HCV antibody, HBV DNA [as applicable], HCV RNA [as applicable]) COVID-19 testing[3]: RT-PCR, Rapid Antigen test or test with similar nature antigen test
	Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) during Screening and EOS/ET visits. Serum or urine pregnancy tests on Day 1 and all dosing visits	If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment

Abbreviations: COVID-19 = Coronavirus disease 2019; DNA = deoxyribonucleic acid; HBsAg = hepatitis B surface antigen; HBV = hepatitis C virus; HCV = hepatitis C virus; HIV= human immunodeficiency virus; TB = tuberculosis; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction

1. Specific leukocyte populations to be reported as counts; percentages are optional.
2. Microscopic examination to be performed if blood or protein is abnormal.
3. COVID-19 testing may be repeated at the discretion of the Investigator.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

NOTE: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- Post-menopausal female
    - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment.

Contraception Guidance:

Male Subjects:

Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male subjects must refrain from donating sperm for the duration of the study and for 12 months after the last dose of study drug.

Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the duration of the study and for 12 months after the last dose of study drug.

Female Subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[1]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized Partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

NOTES:

1 Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

2 Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 12 months after the last dose of study intervention.

Pregnancy Testing

- Woman of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at every dosing visit during the treatment period and at EOS/ET and whenever pregnancy is suspected or at the discretion of the Investigator.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form in the eCRF and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 12 weeks beyond the delivery date. Any termination of the pregnancy will be reported, regardless of foetal state (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.2. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
    - Any female subject who becomes pregnant while participating in the study will discontinue study intervention or will be withdrawn from the study.

10.4 Appendix 4: Genetics

Not applicable.

10.5 Appendix 5: Abbreviations and Trademarks

Abbreviation	Definition
^{18}[F]FDG-PET	Fluorine-18-fluorodeoxyglucose positron emission tomography
ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{0-t}	Area Under the Concentration-Time Curve From Time Zero To The Last Quantifiable Time Point
AUEC	Area Under the Effect Curve
BAb	Binding Antibodies
BORR	Best Overall Response Rate
BSA	Body Surface Area
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CR	Complete Response
CRO	Contract Research Organisation
CRu	Unconfirmed Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Plasma Concentration
DLBCL	Diffuse Large B-Cell Lymphoma
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid

Abbreviation	Definition
DOR	Duration Of Response
DRL	Dr. Reddy's Laboratories
DRL_RI	Proposed Rituximab Biosimilar
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End Of Study
ET	Early termination
EU	European Union
Fc	Fragment Crystallisable
FDA	Food and Drug Administration
FL	Follicular Lymphoma
CCI	CCI CCI
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GELF	Groupe D'Etude des Lymphomes Folliculaires
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPF	High-Power Field
HR	Hazard Ratio
HRT	Hormonal Replacement Therapy
i.v	Intravenous
IB	Investigators' Brochure
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRRs	Infusion-Related Reactions

Abbreviation	Definition
ITT	Intent To Treat
IWRS	Interactive Web Response System
kDa	Kilodaltons
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LTB	Low Tumour Burden
LTB-FL	Low Tumour Burden Follicular Lymphoma
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MR	Maintenance Rituximab
NAb	Neutralising Antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
QTc	Corrected QT Interval
RA	Rheumatoid Arthritis
RMP	Reference Medicinal Product
RNA	Ribonucleic acid
RR	Rituximab Retreatment
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Event
TAT	Turn Around Time
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organisation
WOCBP	Woman Of Childbearing Potential

10.6 Appendix 6: Protocol Amendment History

DOCUMENT HISTORY		
Document	**Version**	**Date**
Amendment 3	Protocol Version 4	04 Nov 2020
Amendment 2	Protocol Version 3	04 Dec 2019
Amendment 1	Protocol Version 2	04 Jan 2019
Original Protocol	Protocol Version 1	25 Oct 2018

Amendment 1, 04 Jan 2019

Overall Rationale for the Amendment:

The protocol was amended based on protocol review non hold comments from the United States Food and Drug Administration (US FDA). One exclusion criterion was added to exclude patients with Central Nervous System involvement by lymphoma. Reference to statistical analysis plan was provided for detailed algorithm for sample size re-estimation and simulations to show that the type-I error rate will be maintained. The method to estimate difference (DRL_RI minus MabThera®) and its 95% Confidence Interval (CI) was updated to use exact Binomial method (Garner W, 2016; and Chan IS, Zhang Z, 1999); accordingly, the references were updated. In addition, a few edits were made for better clarity. The updates made to the protocol as presented in a tabular fashion below to reflect the changes made to the text in the previous version of the protocol (Version 1).

Amendment 2, 04 Dec 2019

Overall Rationale for the Amendment

The protocol was amended based on protocol review and recommendations by the Regulatory Authorities (United States Food and Drug Administration, US FDA). Other administrative changes/edits towards more clarity have also been made. These changes from the previous version of the protocol, are summarized in a tabulated manner below.

Amendment 3, 04 Nov 2020

Overall Rationale for the Amendment

This amendment allows for study inclusion of subjects with past history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection while ensuring that the management practices for this condition are in line with current scientific guidelines.

The protocol is also being amended to reflect contingency measures implemented by the Sponsor in the wake of the COVID-19 pandemic.

A few administrative and minor technical edits towards more clarity have also been made.

The changes from the previous version of the protocol are summarised in a tabulated manner below.

Amendment 1, 04 Jan 2019

S. No	Section Number and Name	Previous Protocol Text (Version 1)	Current Protocol Text (Version 2)	Brief Rationale
1	Sections 1.1 (synopsis) and 5.2; Exclusion Criteria	-	Criterion # 6: Known Central Nervous System (CNS) involvement by lymphoma. (Note: CNS imaging is not required unless clinically indicated.)	Addition of exclusion criterion based on protocol review non-hold comments from US FDA.
2	Section 8.4.9; Regulatory Reporting Requirements for Serious Adverse Events	-	Whenever required applicable local SAE reporting Form will be used (e.g., Appendix XI in India), in addition to eCRF update	Added text for better clarity
3	Section 9.2; Sample Size Determination	Full details will be provided in the SAP.	Full details will be provided in the SAP, *especially* the detailed algorithm for sample size re-estimation and simulations to show that the type-I error rate is maintained	Addition of text based on protocol review non-hold comments from US FDA.
4	Section 9.4.1.1; Analysis of Primary Efficacy Endpoint	The estimated difference (DRL_RI minus MabThera®) and its 95% CI will be obtained using the stratified Miettinen and Nurminen-method. [23]	The estimated difference (DRL_RI minus MabThera®) and its 95% CI will be obtained using the test-based-exact Binomial confidence interval method. [23, 24]	Change in text based on protocol review non-hold comments from US FDA.
5	Section 9.4.2; Safety Analyses	MedDRA (Version 21.1)	MedDRA (Version 21.1 or latest)	Addition of text for using latest available version for Medical dictionary

S. No	Section Number and Name	Previous Protocol Text (Version 1)	Current Protocol Text (Version 2)	Brief Rationale
6	Section 10.1.8; Publication policy	The Sponsor shall retain the title and the right to publish all documentation, records, raw data, specimens or other work product generated pertaining to the study ("Data") conducted by the site (site includes the Investigator and the Institution) as defined in the applicable protocol or study plan or study agreement.	The Sponsor shall retain the title and the right to publish all documentation, records, raw data, specimens or other work product generated pertaining to the study ("Data") conducted by the site (site includes the Investigator and the Institution).	Edited text for better clarity.
7	Section 11; References	Point 23- Miettinen O and Nurminen M. (1985) Comparative analysis of two rates Stat Med.;Apr-Jun;4(2):213-226.	Garner W. (2016). Constructing Confidence intervals for the differences of Binomial proportions in SAS. Available at: https://www.lexjansen.com/wuss/2016/127_Final_Paper_PDF.pdf. Accessed on 04 Jan 2019	Change in reference based on protocol review non-hold comments from US FDA.
8	Section 11; References	-	Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-9	Added new reference based on protocol review non-hold comments from US FDA.

Amendment 2, 04 Dec 2019

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
1.	**Synopsis**	-	Changes made in various sections of the protocol have been reflected in Synopsis	Changes made in various sections of the protocol have been reflected in the Synopsis. Please refer to the section "Synopsis" in the

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
				revised protocol version 3.0 for details.
2.	**Section 1.2; Schema**	Screening period -4 weeks	Screening period -5 weeks	For administrative reasons considering longer turnaround time (TAT) of central histopathology lab evaluation report.
3.	**Table 1-1; Timing for the screening**	Day -28 to -1	Day -35 to -1	For administrative reasons considering longer turnaround time (TAT) of central histopathology lab evaluation report.
4.	**Table 1-1; footnote no.2**	Day 0 and Day 1 can be clubbed into one single day.	Day 0 and Day 1 can be clubbed into one single day. **However, randomisation in IWRS and administration of first dose of study medication should take place on the same day and this will be considered as Day 1.**	For better clarity towards implementation.
5.	**Table 1-1; footnote no.5**	All eligibility criteria must be met before a subject is randomised to study drug. Subjects that do not meet all requirements can be rescreened at the investigator's discretion, following discussion with the Sponsor/designee Medical Monitor	All eligibility criteria must be met **based on the screening assessment** before a subject is randomised to study drug. Subjects that do not meet all requirements can be rescreened at the investigator's discretion, following discussion with the Sponsor/designee Medical Monitor	Added for better clarity and in the interest of subject safety.
6.	**Table 1-1; footnote no.6**	Subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site. Subjects must have sufficient tissue samples available for the central pathology review (obtained on or within 6 months prior to the screening date) and a centrally-confirmed diagnosis prior to being randomised.	Subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site. Subjects must have sufficient tissue samples available for the central pathology review (obtained on or within **12** months prior to the screening date) and a centrally-confirmed diagnosis prior to being randomised.	Added in the interest of subject, invasive nature of procedure and indolent course of disease under study.
7.	**Table 1-1; footnote no.8**	Temperature, blood pressure, pulse rate, and respiratory rate will be recorded at each time point. Vital signs will be monitored every	Temperature, blood pressure, pulse rate, and respiratory rate will be recorded at each time point. Vital signs will be monitored every	For better implementation and clarity.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
		30 minutes during the course of the treatment administration and at end of infusion or more frequently as necessary.	30 minutes **(±5 minutes)** during the course of the treatment administration and at end of infusion or more frequently as necessary.	
8.	**Table 1-1; footnote no.11**	Tuberculosis testing (QuantiFERON®-TB Gold-in-Tube test - QFT-GIT or QuantiFERON®-TB Gold Plus) is requested only if it is required by local regulations or practice	**If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.**	For better clarity towards implementation.
9.	**Table 1-1; footnote no.13**	Tumour assessments for the purpose of assessing subject eligibility (with central imaging confirmation) and medical care will be performed by the investigational site at Screening, Weeks 12, 28, and 52 (EOS/ET Visit) by reviewing CT scans (Neck, chest, abdomen, and pelvis) with contrast. Computed tomography scans obtained up to **4 weeks** prior to the first administration of study drug may be used for determining study eligibility provided they are of adequate quality for subsequent central review……..Assessments are NOT to be scheduled based on the previous imaging time point, but rather Day 1 should be used as the Baseline when calculating when the on-study tumour assessments are to be performed (with consideration of visit windows).	Tumour assessments for the purpose of assessing subject eligibility (with central imaging confirmation) and medical care will be performed by the investigational site at Screening, Weeks 12, 28, and 52 (EOS/ET Visit) by reviewing CT scans (Neck, chest, abdomen, and pelvis) with contrast. Computed tomography scans obtained up to **6 weeks** prior to the first administration of study drug may be used for determining study eligibility provided they are of adequate quality for subsequent central review……Assessments are NOT to be scheduled based on the previous imaging time point, but rather Day 1 should be used as the Baseline when calculating when the on-study tumour assessments are to be performed (with consideration of visit windows).	For implementing uniformity of timings of imaging modalities allowed for the purpose of eligibility.
10.	**Table 1-1; footnote 15**	Bone marrow biopsies or aspirations performed up to 6 weeks prior to the first administration of study drug may be used. Additional bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.	Bone marrow biopsies or aspirations performed up **to 12 weeks** prior to the first administration of study drug may be used. Additional bone marrow biopsies are required for any subject who has a response of CR at an evaluation point and either had a bone marrow examination positive for FL at Screening or shows new abnormalities in the peripheral blood counts or blood smear that clinically indicates a bone marrow evaluation is required.	In the interest of subject considering invasive nature of the biopsies/aspirations and indolent nature of the disease under study.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
11.	**Table 1-1; footnote 16**	All the baseline assessments must be reviewed by the investigators for final eligibility assessment before randomisation of the subject	**Before randomisation of the subject,** all the baseline assessments must be reviewed by the investigators for **suitability of starting the study treatment.**	For better clarity.
12.	**Section 2.2. Background; subsection 2.2.3 Efficacy of Rituximab in Low Tumour Burden Follicular Lymphoma**	A total of 463 subjects were randomised (187 Arm A, 84 Arm B, and 192 Arm C) with 95% of subjects having low tumour burden (LTB) according to the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria.	A total of 463 subjects were randomised (187 Arm A, 84 Arm B, and 192 Arm C) with 95% of subjects having low tumour burden (LTB) according to **predefined criteria** similar to the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria.	For better clarity.
13.	**A secondary objective in the Section 3; Objectives and endpoints**	To compare the PFS, ORR at Week 12, OS and duration of response (DOR) of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL.	To compare the ORR at Week 12, **CR at 28 weeks** duration of response (DOR), PFS and OS of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL.	Added to comply with Regulatory Authority advice.
14.	**Secondary endpoint in the Section 3; Objectives and endpoints**	-	**Complete Response (CR) rate at Month 7 (Week 28).**	Added to comply with Regulatory Authority advice.
15.	**Secondary endpoint in the Section 3; Objectives and endpoints**	• Progression-free survival defined as the time from date of randomisation to the date of documented progressive disease (PD) or death due to any cause. • Overall response rate at Week 12 based on central radiology review in accordance with published response criteria for malignant lymphoma [13]. • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/End of Study (EOS).	• Overall response rate at Week 12 based on central radiology review in accordance with published response criteria for malignant lymphoma[13]. • Complete Response (CR) rate at Month 7 (Week 28). • Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS.	Rearrangement of the secondary endpoints to follow the chronological order in which they are determined in the Study.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
		• Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS. • Adverse events, clinical laboratory values, vital signs, and electrocardiogram (ECG) • Anti-rituximab antibodies and their relationship with other outcome measures.	• Progression-free survival defined as the time from date of randomisation to the date of documented progressive disease (PD) or death due to any cause. • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/End of Study (EOS). • Adverse events, clinical laboratory values, vital signs, and electrocardiogram (ECG) • Anti-rituximab antibodies and their relationship with other outcome measures.	
16.	**Section 4.1.1; Description**	The study will enrol subjects with CD20-positive, LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the GELF criteria.[3]	The study will enrol subjects with CD20-positive, LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the GELF **based** criteria.[3, 9]	For better clarity.
17.	**Section 4.1.1; Description**	Randomisation will be stratified by low, medium, and high-risk subjects using the CCI CCI (CCI, CCI), as well as by tumour grade and geographical area.	Randomisation will be stratified by low, medium, and high-risk subjects using the CCI CCI (CCI, CCI), as well as by tumour grade **(1-2 Vs. 3a)** and geographical area **(USA, Europe and Asia-Pacific region).**	For better clarity and to further specify the randomization strata.
18.	**Section 4.2; Schedule of assessments**	The study will enrol subjects with LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the GELF criteria. [9,16]	The study will enrol subjects with LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to GELF **based** criteria. [9, 16]	For better clarity.
19.	**Section 4.3; Scientific rationale for study design**	Low tumour burden will be assessed according to the GELF criteria.[9,16]A serum LDH level within normal limits will be required for enrolment as LDH is an important prognostic factor in FL.	Low tumour burden will be assessed according to GELF **based** criteria. [9, 16]A serum LDH level within normal limits will be required for enrolment as LDH is an important prognostic factor in FL.	For better clarity.
20.	**Section 5.1; inclusion criterion 3**	Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF criteria. Subjects must have tissue available for the	Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF-**based** criteria. Subjects must have tissue	For better clarity.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
		central pathology review and a centrally-confirmed diagnosis prior to being randomised.	available for the central pathology review and a centrally-confirmed diagnosis prior to being randomised.	
21.	**Section 5.1; inclusion criterion 4**	Ann Arbor Stage II to IV of histological Grade 1, 2, or 3a (Section 10.1.14).	Ann Arbor Stage II to IV (Section 10.1.14).	Deleted repetitive text.
22.	**Section 5.1; inclusion criterion 6**	As per central radiological assessment, involvement of <3 nodal sites with diameter measuring >3 cm	As per central radiological assessment, involvement of **≤3 nodal** sites with diameter measuring >3 cm	To add clarity and to ensure the inclusion criteria are in alignment with those in the reference documents from which the design data (and thus the study's statistical assumptions) were obtained.
23.	**Section 5.2; exclusion criterion 8**	Prior malignancy other than non-melanoma skin cancer or intraepithelial cervical neoplasia, successfully treated more than 1 year before study inclusion.	Prior malignancy **(including recurrence) within 5 years of screening,** other than non-melanoma skin cancer or intraepithelial cervical neoplasia, **which should have been** successfully treated more than 1 year before study inclusion.	Added clarity with respect to prior malignancies.
24.	**Section 5.2 exclusion criterion 10**	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 drug (Day 1). Tuberculosis testing (QuantiFERON®-TB Gold-in-Tube test - QFT-GIT or QuantiFERON®-TB Gold Plus) is requested only if it is required by local regulations or practice.	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 drug (Day 1). **If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.**	To add clarity for better implementation.
25.	**Section 5.2 exclusion criterion 19**	Subject has been previously enrolled and/or randomised in this study.	Subject has been previously randomised in this study.	For better clarity.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
26.	**Section 6.2; study drugs administered**	Subjects will be randomised in a 1:1 ratio to one of the 2 study treatment arms taking into account stratification by low-, medium-, and high-risk subjects using the CCI index (CCI), tumour grade, and geographical area:	Subjects will be randomised in a 1:1 ratio to one of the 2 study treatment arms taking into account stratification by low-, medium-, and high-risk subjects using the CCI index (CCI), tumour grade**(1-2 Vs. 3a),** and geographical area **(USA, Europe and Asia-Pacific region):**	For better clarity and to elaborate on the randomization strata.
27.	**Section 6.4; Measures to minimise bias: Randomisation and Blinding**	The randomisation codes will be computer-generated and kept by a statistician independent from the project team. Randomisation will be stratified by low, medium, and high-risk subjects using CCI (CCI), as well as by tumour grade and geographical area.	The randomisation codes will be computer-generated and kept by a statistician independent from the project team. Randomisation will be stratified by low, medium, and high-risk subjects using CCI (CCI), as well as by tumour grade **(1-2 Vs. 3a)** and geographical area **(USA, Europe and Asia-Pacific region).**	For better clarity and to elaborate on the randomization strata.
28.	**Section 6.8; Dose modification or delays**	Any delays beyond what is mentioned above should be discussed with Contract Research Organisation (CRO) Medical Monitor.	Any delays beyond what is mentioned above should be discussed in detail. If the out of window visit is on account of an adverse event or for safety related reasons, discussion with Medical Monitor (MM) is required, hence please contact your CRO MM under these circumstances. And if any social / other reasons lead to an out of window visit, then please document the reason for visit delay by adding a note/ short description in eCRF. Every out of window visit (irrespective of the reason) should be documented as a deviation.	More detailed provided for better clarity.
29.	**Section 8.1.1**	**8.1.1 Screening (Day -28 to -1)** Subjects will undergo a Screening Visit at least 0 days, but not more than 28 days prior to the planned first day of blinded study drug.	**8.1.1 Screening (Day -35 to -1)** Subjects will undergo a Screening Visit at least 0 days, but not more than 35 days prior to the planned first day of blinded study drug.	For administrative reasons considering long turnaround time (TAT) of central histopathology lab evaluation report.
30.	**Section 8.1.1 (In chronological order of the assessments)**	5. Histological confirmation of diagnosis (subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site). Subjects must have sufficient tissue samples available for the central pathology	5. Histological confirmation of diagnosis (subjects can be screened for the study based on a diagnosis of CD20-positive, low burden FL confirmed at the investigational site). Subjects must have sufficient tissue samples available for the central pathology	Added in the interest of the subject considering invasive nature of procedure and indolent

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
		review (obtained on or within 6 months prior to the screening date), and a centrally-confirmed diagnosis prior to being randomised.	review (obtained on or within **12 months** prior to the screening date), and a centrally-confirmed diagnosis prior to being randomised.	nature of disease under study.
31.	**Section 8.1.1 (In chronological order of the assessments)**	18. Bone marrow biopsy (if no previous biopsy within the last 6 weeks before dosing is available). Procedures can be performed locally.	18. Bone marrow biopsy (if no previous biopsy within the last **12 weeks** before dosing is available). Procedures can be performed locally.	For better implementation of the study procedures.
32.	**Section 8.1.2 Treatment period**	Eligible subjects will return to the study site for the Baseline (Day 0 to Day 1) Visit. Subjects must satisfy inclusion/exclusion criteria in order to be eligible for randomisation. All the baseline assessments must be reviewed by the investigators for final eligibility assessment before randomisation of the subject.	Eligible subjects will return to the study site for the Baseline (Day 0 to Day 1) Visit. Subjects must satisfy inclusion/exclusion criteria in order to be eligible for randomisation. **Before randomisation of the subject**, all the baseline assessments must be reviewed by the investigators for **suitability of starting study treatment.**	For better clarity.
33.	**Section 8.1.2 Treatment period**	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.	Baseline procedures and assessments should be conducted in chronological order as follows: 1. Re-review subject eligibility (inclusion and exclusion) criteria **based on the screening assessment** to ensure that the subject continues to be eligible for inclusion into the study.	For better implementation and clarity.
34.	**Section 8.3.2; Vital Signs**	Vital signs are to be obtained prior to each study drug infusion, every 30 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's judgment.	Vital signs are to be obtained prior to each study drug 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's judgment.	For better implementation and clarity.

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
35.	**Section 8.3.4; Clinical safety laboratory assessments**	Other screening tests: FSH (as needed in women of non-childbearing potential only), serum β-hCG, and urine pregnancy test (for women of childbearing potential), serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, and HCV antibody). TB screening (QuantiFERON®-TB Gold-in-Tube test - QFT-GIT or QuantiFERON®-TB Gold Plus) is requested only if it is required by local regulations or practice.	Other screening tests: FSH (as needed in women of non-childbearing potential only e.g., women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history), serum β-hCG, and urine pregnancy test (for women of childbearing potential), serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, and HCV antibody). **If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.**	To add clarity for better implementation.
36.	**Section 9.1.1; General principles**	-	**An additional analysis may be performed based on country specific requests/requirements by the relevant Authorities**	For better clarity.
37.	**Section 9.4.1.2;**	• Progression-free survival defined as the time from date of randomisation to the date of documented PD or death due to any cause. • Overall response rate at Week 12 based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/EOS. • Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS	Secondary efficacy endpoints include the following: • Overall response rate at Week 12 based on central radiology review in accordance with the response criteria for malignant lymphoma.[13] • **Complete Response (CR) rate at Month 7 (Week 28).** • Duration of response defined as the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of PD or to death due to any cause up to 52 weeks/EOS.	Addition of secondary end point as detailed in change no. 13 above and the rearrangement of the endpoints to follow the chronological order in which they are determined in the Study

S. No.	Section number and Name	Previous Protocol V2.0 dated 04 January 2019	Current Protocol V3.0 dated 04 December 2019	Brief Rationale
			• Progression-free survival defined as the time from date of randomisation to the date of documented PD or death due to any cause. • Overall survival defined as the time from date of randomisation to the date of death from any cause up to 52 weeks/EOS.	
38.	**Section 10.1.6 Data monitoring committee**	-	**Section 10.1.6 Data Monitoring Committee** **An independent Data Monitoring Committee (DMC) will be established for the study, and operate according to procedures described in the DMC Charter. All meeting proceedings will be documented.**	Added to reflect set up of DMC for the study. The numbers of subsequent subsection numbers till 10.1.14 are changed.
39.	**Table 10.4 Parameters for other screening tests**	Follicle stimulating hormone (as needed in women of non-childbearing potential only. Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	Follicle stimulating hormone (as needed in women of non-childbearing potential only **e.g. women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidences based on clinical assessment and medical history)** Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	To add clarity for better implementation.
40.	**Table 10-4 Parameters for other screening tests**	TB screening (QuantiFERON®-TB Gold-in-Tube test - QFT-GIT or QuantiFERON®-TB Gold Plus) is requested only if it is required by local regulations or practice	**If latent TB is suspected based on clinical or epidemiological grounds, it should be further investigated using the tuberculosis testing as appropriate following local practice or investigator judgment.**	To add clarity for better implementation.
41.	**Section 10.5 Appendix 5 Abbreviations and trademarks**	-	**DMC- Data Monitoring Committee** **TAT- Turn Around Time**	List of abbreviations updated.

Amendment 3, 04 Nov 2020

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
1.	**Key Study Personnel; Medical Monitors**	PPD	PPD	To align with updated list of medical monitors.
2	**Synopsis**	-	Changes made in various sections of the protocol have been reflected in Synopsis	Changes made in various sections of the protocol have been reflected in the Synopsis. Please refer to Section 1.1 Synopsis in the revised protocol version 4.0 for details.
3	**Table 1-1; Viral disease screening**	Screening	Screening**, Week 12, 20, 28, 36, Week 44, and Week 52**	For subjects with history of hepatitis B requiring HBV DNA and subjects with history of Hepatitis C requiring HCV RNA at Screening.
4	**Table 1-1; footnote no.9**	Women of childbearing potential will have a serum pregnancy test during screening and a urine pregnancy test on Day 1 prior to randomisation, and all subsequent study drug dosing visits.	Women of childbearing potential will have a serum pregnancy test during Screening and **urine or serum** pregnancy tests on Day 1 prior to randomisation, and all subsequent study drug dosing visits.	Edited for improved clarity and implementation.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
5	**Table 1-1; footnote no.12**	Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus, and/or human immunodeficiency virus to be conducted by local laboratory	Hepatitis B surface antigen, hepatitis B core antibody, **HBV DNA (as applicable), HCV RNA (as applicable),** hepatitis C virus, and/or human immunodeficiency virus to be conducted by local laboratory. **HBV DNA at Screening, Week 12 and all visits from Week 12 onwards (only for subjects with history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection). Additional monitoring/management of subjects who were HCV antibody positive (and HCV RNA negative) at Screening should be done in accordance with local practice and standard of care.**	To allows for study inclusion of subjects with past history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection and subjects with history of hepatitis C while ensuring that the management practices for this condition are in line with current scientific guidelines.
6	**Table 1-1; COVID-19 testing**	-	**Baseline**	For adherence with contingency measures implemented during the COVID-19 pandemic.
7	**Table 1-1; COVID-19 related screening questionnaire**	-	**Every Visit**	For adherence with contingency measures implemented during the COVID-19 pandemic.
8	**Table 1-1; footnote no.21**	-	**COVID-19 testing (RT-PCR, Rapid Antigen test or test with similar nature antigen test but no antibody test) to be performed as close as possible but no more than 4 days before first dose administration. COVID-19 testing may be repeated at the discretion of the Investigator. Subjects should be randomised only after negative COVID-19 test result.**	For adherence with contingency measures implemented during the COVID-19 pandemic in the interest of subject safety.
9	**Section 3 Objectives and Endpoints; Secondary endpoints**	Anti-DRL_RI antibodies	Anti-**rituximab** antibodies	Updated to reflect the actual assessment and better clarity.
10	**Section 4.1.1 Description**	-	coronavirus disease 2019 (COVID-19) testing at screening and as deemed appropriate by the Investigator at any time during the study.	For consistency and clarity.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
			Subjects with a prior history of hepatitis B infection or serological tests suggestive of previous hepatitis B infection will continue to receive hepatitis B virus (HBV) antiviral prophylaxis therapy for at least 12 months post last dose of rituximab in the study and will be monitored and reported for reactivation for up to 24 months following completion of rituximab therapy.	
11	**Section 4.5 End of Study Definition**	Clinical assessments will include the following: Physical examination (including weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral body temperature).	Clinical assessments will include the following: Physical examination (including weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral**, axillary, or tympanic** body temperature).	For consistency and clarity.
12	**Section 5.1 Inclusion Criteria; Inclusion criterion no.3**	Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF based criteria. Subjects must have tissue available for the central pathology review and a centrally-confirmed diagnosis prior to being randomised. Should a subject be eligible as per the central imaging review but not as per the Study Centre Review the subject will be considered eligible if confirmed both by the Investigator and the Medical Monitor (MM). For any other disagreement in eligibility the subject will be considered ineligible.	Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF based criteria. Subjects must have **sufficient** tissue **samples** available for the central pathology review **(** Section 8.1.1**),** and a centrally-confirmed diagnosis prior to being randomised. Should a subject be eligible as per the central imaging review but not as per the Study Centre Review the subject will be considered eligible if confirmed both by the Investigator and the Medical Monitor (MM). For any other disagreement in eligibility the subject will be considered ineligible.	Updated for clarity and consistency with rest of the protocol.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
13	**Section 5.2 Exclusion Criteria; Exclusion criterion no.9**	Subjects with any of the following: known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV).	Subjects with any of the following: known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)~~, hepatitis B surface antigen (HBsAg) positive or hepatitis B core antibody positive, hepatitis C virus (HCV) antibody positive~~.	Separate exclusion criterion (no.10) for known seropositivity or history of active hepatitis B and hepatitis C infections was created.
14	**Section 5.2 Exclusion Criteria; Exclusion criterion no.10**	-	**Subjects with positive serological test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C virus (HCV) antibody can only be included in the study if any of the following is fulfilled.** • **Subjects with a negative HBsAg and positive total HBcAb must have a HBV deoxyribonucleic acid (DNA) level <20 IU/mL (or 112 copies/mL) by polymerase chain reaction (PCR) to participate in the study. In addition, it is required for these subjects to follow consultation with a hepatologist / relevant expert regarding initiation, monitoring, and use of HBV antiviral therapy and the subject must be willing to undergo PCR HBV DNA testing during treatment and agree to receive treatment as indicated. HBV DNA re-test will be performed as per the schedule of assessments (ref. table no. 1-1) and further as needed, at the discretion of the Investigator.** • **Subjects with a positive test because of HBV vaccination may be included (i.e., HBsAg negative, anti-HBs+, HBcAb–).** • **Subjects positive for HCV antibody are eligible only if the PCR test for HCV ribonucleic acid (RNA) is negative.**	To allows for study inclusion of subjects with past history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection and subjects with history of hepatitis C while ensuring that the management practices for this condition are in line with current scientific guidelines.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
15	**Section 5.2 Exclusion Criteria; Exclusion criterion no.12**	Subjects who have received a live vaccine within last or non-live vaccine within 4 weeks of the first administration of study drug.	Subjects who have received a live vaccine within last 3 months or non-live vaccine within 4 weeks of the first administration of study drug. **[Note: A need may arise for trial subjects to receive vaccine against COVID-19 while being a part of the study. All such decisions will be taken at the discretion of the Investigator in consultation with the CRO / Sponsor after due consideration to subjects' safety, national health policy of the respective country and overall need by the subject for such vaccine during the time of study participation].**	Updated for adherence with contingency measures implemented during the COVID-19 pandemic.
16	**Section 6 Study Intervention**	Section 6.9 The End of the Study	Section 6.9 **Study medication access after t**he End of the Study	Sub-heading updated for clarity.
17	**Section 6 Study Intervention**	Section 6.10 Management of Hepatitis Reactivation and Other Infections during Rituximab Therapy	**Section 6.10 Guidance for hepatitis B and hepatitis C seropositive subjects**	Sub-heading updated for clarity.
18	**Section 6.10 Guidance for hepatitis B and hepatitis C seropositive subjects**	-	**Subjects who show evidence of prior hepatitis B infection may participate in the study following consultation with a Hepatologist / relevant expert regarding monitoring and use of HBV antiviral therapy, and provided that subjects agree to receive and comply with HBV testing and hepatitis B prophylactic therapy as recommended by the Investigator, treating hepatologist, or relevant expert. HBV re-test will be performed as per schedule of assessment (see Table 1–1) and further at the discretion of the Investigator.** **Additional monitoring/management of subjects who had HCV antibody positive (and HCV RNA negative) at Screening should be done in accordance with local practice and standard of care.** **Subjects will continue to receive HBV antiviral prophylaxis therapy for at least 12 months post last dose of rituximab in the study (i.e. 36 weeks, or earlier in case of ET), and will be monitored as recommended by hepatitis experts in accordance**	Added to ensure safety of subjects who show evidence of prior hepatitis B and hepatitis C infection as per the management practices for this condition in line with the current scientific guidelines.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
			with local practice and guidelines. HBV reactivation will be monitored and reported for up to 24 months following completion of rituximab therapy. If any subject develops reactivation of HBV or any other significant infections while on rituximab, the Investigator should immediately discontinue study drug, consult with hepatitis experts, and institute appropriate treatment. For details and management of other infections, refer to the current marketed rituximab prescribing information. **It will be the Investigator's responsibility to ensure compliance to the antiviral treatment, regular follow-up for monitoring (i.e. laboratory tests, clinical examination, AE evaluation) with the Hepatologist / relevant expert of Hepatitis B seropositive subjects and reporting of any reactivation events to the Sponsor immediately during and post study follow up period of 24 months post last dose of rituximab. The investigator has to periodically update to the Sponsor about all such follow-up visits, treatment compliance with antiviral and other medications, tests results, and Hepatitis B reactivation for up to 24 months post last study dose of rituximab. Detailed procedure and the needed documentation to ensure compliance to post study follow up and measures will be outlined in an amended study agreement between the Sponsor / Designee and the Investigator.** **Post study period of 52 weeks, all safety related events to be reported directly to the Sponsor's e mail address- pharmacovigilance@drreddys.com.**	
19	**Section 8.1 Study Assessments**	-	**Completion of a COVID-19 related screening questionnaire.**	Added to each visit for adherence with contingency measures implemented during the COVID-19 pandemic.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
20	**Section 8.1 Study Assessments**	Clinical assessments will include the following: Physical examination (including a thorough assessment of the lymph nodes, liver, spleen, height and weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral temperature).	Clinical assessments will include the following: Physical examination (including a thorough assessment of the lymph nodes, liver, spleen, height and weight), vital signs measurement (blood pressure, heart rate, respiration rate, and oral**, axillary, or tympanic body** temperature).	Added to each visit for clarity.
21	**Section 8.1.1 Screening (Day -35 to -1)**	The proposed chronological order of the assessments below should be followed.	The ~~proposed chronological order of the~~ assessments ~~below~~ **suggested to be conducted in the following chronological order** ~~should be followed~~.	Edited for clarity.
22	**Section 8.1.1 Screening (Day -35 to -1); assessment no.14**	Viral disease screening: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), HCV, and/or HIV.	Viral disease screening: ~~hepatitis B surface antigen (~~HBsAg~~)~~, **HBcAb**~~hepatitis B core antibody (anti-HBc)~~, **HBV DNA (as applicable), HCV RNA (as applicable),** HCV, and HIV.	Added for improved implementation and clarity.
23	**Section 8.1 Study Assessments; Maintenance Treatment Period, Follow-up Period, and End of Study**	-	**Viral disease screening: HBV DNA (as applicable) and HCV RNA (as applicable).**	Added for improved implementation and clarity.
24	**Section 8.1.2 Treatment Period; Baseline Visit**	Baseline procedures and assessments should be conducted in chronological order as follows:	Baseline procedures and assessments **suggested** ~~should~~ **to** be conducted in **the following** chronological order ~~as follows~~:	Edited for improved clarity and implementation.
25	**Section 8.1.2 Treatment Period; Baseline Visit (Day 0 to Day 1, prior to randomization and administration of the study drug)**	-	**COVID-19 testing (RT-PCR, Rapid Antigen test or test with similar nature antigen test but no antibody test) to be performed as close as possible but no more than 4 days before first dose administration. Thus, COVID-19 testing may also be performed during the last few days of the screening window, ensuring maximum time gap of 4 days between first dose of the study drug and COVID-19 testing.**	For clarity and adherence with contingency measures implemented during the COVID-19 pandemic and in the interest of subject safety.
26	**Section 8.1.2 Treatment Period; Baseline Visit (Day 0 to Day 1, prior to**	Urine pregnancy test (performed locally, according to local practice).	Urine **or serum** pregnancy test (performed locally, according to local practice).	Added for improved implementation and clarity.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
	randomization and administration of the study drug)			
27	**Section 8.1.2 Treatment Period; Study Days 8, 15 and 22 (Week 2 to Week 4 ± 2 days)**	Urine pregnancy test (performed locally, according to local practice).	Urine **or serum** pregnancy test (performed locally, according to local practice).	Added for improved implementation and clarity.
28	**Section 8.1.2 Treatment Period; Week 12 to Week 36 ± 7 days**	Urine pregnancy test (performed locally, according to local practice).	Urine **or serum** pregnancy test (performed locally, according to local practice).	Added for improved implementation and clarity.
29	**Section 8.1.4 End of Study;**	Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, urinalysis, and pregnancy tests.	Clinical laboratory tests: Blood and urine samples will be taken for haematology, biochemistry, coagulation, urinalysis, and **serum** pregnancy tests.	Added for improved implementation and clarity.
30	**Section 8.3.2 Vital Signs**	Vital signs, including heart rate, blood pressure, respiratory rate, and oral or tympanic body temperature, will be measured as detailed in Table 1–1 and in the event of an infusion reaction.	Vital signs, including heart rate, blood pressure, respiratory rate, and oral**, axillary** or tympanic body temperature, will be measured as detailed in Table 1–1 and in the event of an infusion reaction.	Added for improved implementation and clarity.
31	**Section 8.3.4 Clinical Safety Laboratory Assessments**	Urine pregnancy test will be conducted on Day 1 prior to randomisation, and all subsequent study drug dosing visits. Urinalysis (by dipstick): specific gravity, pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase.	Urine **or serum** pregnancy tests will be conducted on Day 1 prior to randomisation, and all subsequent study drug dosing visits. Urinalysis (by dipstick **or any other method**): specific gravity, pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase **or leukocytes**.	Added for improved implementation and clarity.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
32	**Section 8.5 Study Conduct During the COVID-19 Pandemic**	-	**Coronavirus disease 2019 (COVID-19) is a viral illness caused by the novel coronavirus (also called SARS-CoV-2) and has impacted most of the countries across the globe. It was declared as a global public health emergency by the WHO on 30 Jan 2020. and declared as a pandemic on 11 Mar 2020. This pandemic has impacted the conduct of clinical trials in various ways.**	For clarity and adherence with contingency measures implemented during the COVID-19 pandemic.

33	**Section 8.5.1 Contingency Measures Implemented During the COVID-19 Pandemic**	-	**In the current global outbreak of coronavirus disease 2019 (COVID-19), Dr. Reddy's Laboratories (DRL) has recognized the potential impact on the conduct of RI-01-006 study due to various reasons. Considering that the safety of trial participant is paramount, DRL has initiated various contingency measures for the well-being of subjects and in order to ensure compliance with guidance issued by various regulatory agencies:**
			• **COVID-19 protective measures: Recommendation to study sites to inform and encourage all study subjects to practice COVID-19 basic protective measures at all times.**
			• **COVID-19 testing and COVID-19 related screening questionnaire:**
			  ○ **Each subject being randomized will undergo COVID-19 testing (preferably RT PCR) and only subjects with confirmed negative test results will be administered the study drug. Additional testing for COVID-19 during the course of study may be performed at the discretion of the Investigator. All such test results will be documented appropriately in CRF.**
			  ○ **COVID-19 related screening questionnaire to rule out active**
				For clarity and adherence with contingency measures implemented during the COVID-19 pandemic.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
			COVID-19 infection as well as to evaluate further if potential study subjects are at risk of acquiring COVID-19 at screening visit and during the study period. Study drug will be administered only in those subjects who are considered at no-risk by the Investigator based on this evaluation. • **Inform Consent Document (ICD) amended to include possible risks related to COVID-19 and rituximab treatment. All ongoing subjects will undergo re-consent with a newer version of the ICD, after approval from a respective ethics committee (EC). All new subjects being screened will be asked to give their consent using the newer version of the ICD.** • **Advise study sites to prioritize subjects' safety and priority care in the event of COVID-19 infection.** • **The investigator must stop rituximab treatment if any of the study subjects acquire COVID-19 infection while in the study. Re-institution of therapy should be done after careful benefit risk assessment by the Investigator once the subject has been confirmed as cured of COVID-19 with appropriate laboratory testing.** • **The Investigator is encouraged to do telephonic inquiry of study subjects to know about their overall well-being, adverse events, including suspected COVID-19 symptoms, concomitant medications etc.** • **COVID-19 events in the study are to be considered as "Events of Special Interest (EOSI)" and all relevant detailed**	

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
			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 as an SAE. **All details of remote monitoring, including discussion with sites on informed consent process, subject eligibility, review of central lab data, review of data entry, query resolution, pending actions, review of protocol deviations etc., have been captured in the monitoring plan, as applicable. Detailed information about the type of data to be collected, handling of missing data or assessments/procedures 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 and additional safety contingency measures will be generated based on the available data, if required. Corresponding details will be mentioned in the SAP. Based on the evolving COVID-19 pandemic, the Sponsor will revisit these contingency measures for any further changes, or for their continuation/discontinuation, as needed, while ensuring subject safety and trial data integrity throughout the conduct of the study.**	
34	**Section 9.2 Sample Size Determination**	[redacted] CCI [redacted]	[redacted] CCI [redacted]	For better administrative flexibility.
35	**Section 9.4.5 Pharmacodynamics Assessment**	-	**On the basis of B-cell counts a population pharmacodynamics evaluation including population pharmacokinetics-pharmacodynamics evaluation**	Added for clarity.

S. No.	Section number and Name	Previous Protocol V3.0 dated 04 December 2019	Current Protocol V4.0 dated 04 November 2020	Brief Rationale
			might be performed which will be evaluated in a separate analysis plan.	
36	**Section 10.2 Appendix 2: Clinical Laboratory Tests**	-	Changes made in various sections of the protocol have been reflected in Appendix 2.	Changes made in various sections of the protocol have been reflected in the Appendix 2. Please refer to Section 10.2 Appendix 2: Clinical Laboratory Tests s in the revised protocol version 4.0 for details.
37	**Section 10.6 Appendix 6: Protocol Amendment History**	-	**Moved previous summary of changes table to this section**	Moved previous summary of changes table to this section.
38	**Section 10.7 Appendix 7: COVID-19 Related Screening Questionnaire**	-	**COVID-19 related screening questionnaire was inserted in Appendix 7.**	For adherence with contingency measures implemented during the COVID-19 pandemic in the interest of subject safety.
39	**Whole document**	-	Abbreviations, administrative information, editorial changes, and/or style or formatting revisions were made.	For improving clarity and consistency throughout the protocol.

10.7 Appendix 7: COVID-19 Related Screening Questionnaire

Study # RI-01-006
COVID-19 Related Screening Questionnaire

Please complete this form at Screening, Baseline and every subsequent study visit before every dosing (please refer schedule of assessment in protocol).

Please send completed form to the PAREXEL CRA/Medical Monitor along with Patient Enrollment Form for screening visit only. For subsequent visits, please keep completed form along with Patient's source documents for the visit.

Patient ID / Initials: _____ / _____
Visit No. (Tick applicable): Screening / Wk 1 / Wk 2 / Wk 3 / Wk 4 / Wk 8 / Wk 12 / Wk 20 / Wk 28 / Wk 36 / Wk 44 / Wk 52 / Early Termination/ Unscheduled visit
Date of Visit: _____/ _____/ _____

Q. No.	Questions	Responses
1	Does the patient have any COVID-19 signs / symptoms?	☐ Yes / ☐ No
2	Have any of the patient's close contacts been diagnosed with COVID-19 in the last two months / since last visit?	☐ Yes / ☐ No
3	Considering the age of the patient and co-morbidities (if any), do you believe rituximab treatment will pose an additional risk to the patient related to COVID-19?	☐ Yes / ☐ No
4	Looking at the overall COVID-19 pandemic in your country and city, do you see any challenges with the protocol mandated weekly dosing and compliance with other study procedures (e.g., hospital visits, investigations, imaging etc.)?	☐ Yes / ☐ No
5	Do you foresee any challenges in the availability of the study team for conducting ongoing patient visits?	☐ Yes / ☐ No
6	If tests are available, has the patient tested for COVID-19 at screening? *(RT-PCR, Rapid Antigen test or test with similar nature antigen test but no antibody test)* If tested, Name of Test - _____ Result of the COVID-19 testing	☐ Yes / ☐ No ☐ Positive ☐ Negative

*If any response to the above questions (No. 1 - 5) is YES **or** Positive for question No. 6, we request you to put temporary hold on your decision to screen / randomize / dose the patient and contact your site CRA or Medical Monitor.*

Investigator Name and Title (print):	
Signature:	Date: / / (DD/MMM/YYYY)

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Investigator Agreement Page

Declaration of the Investigator

Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera® in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD) 20-Positive, Low Tumour Burden Follicular Lymphoma.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic case report form, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC or IRB, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol version 5.0 dated 27 Oct 2021.

Responsible Investigator of the local study centre

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number