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

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Parexel International

Dr. Reddy's Laboratories S.A

Protocol RI-01-006

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 Tumor Burden Follicular Lymphoma

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SPONSOR SIGNATURE PAGE

Approved by:

PPD

18-Aug-22

Date

PPD

Dr. Reddy's Laboratories

Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with CCI CCI and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	20-Mar-19	New Document
2.0	23-Apr-21	Amendment based on Study Protocol Amendments 2 and 3
3.0	28-Jan-22	Amendment based on Study Protocol Amendment 5 (in particular due to implementation of the ICH E9R1 addendum)
4.0	18-Aug-22	Amendment based on FDA feedback received on previous version of analysis plan submitted to agency for review.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUEC	Area Under the Effect Curve
BAb	Binding Antibodies
B-cell	Blood Cell
BMP	Blinding Maintenance Plan
BOR	Best Overall Response
BORR	Best Overall Response Rate
BSA	Body Surface Area
BSSR	Blinded Sample Size Re-estimation
CD	Cluster of Differentiation
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRu	Unconfirmed Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Plasma Concentration
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DOR	Duration of Response
DNA	Deoxyribonucleic Acid
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
E_{max}	Maximum Effect or Response
EOS	End of Study
EOSI	Events of Special Interest

ET	Early termination
FDA	Food and Drug Administration
FDG-PET	Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography
FL	Follicular Lymphoma
CCI [redacted]	CCI [redacted]
GCP	Good Clinical Practice
GELF	Groupe D'Etude des Lymphomes Folliculaires
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
i.v.	Intravenous
ICEs	Intercurrent Events
ICF	Informed Consent Form
IP	Investigational Product
IRR	Infusion-Related Reaction
ITT	Intention to Treat
IWRS	Interactive Web Response System
kDa	Kilodaltons
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LTB	Low Tumour Burden
LTB-FL	Low Tumour Burden Follicular Lymphoma
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralising Antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDS	Pharmacodynamic Analysis Set
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic

PKS	Pharmacokinetic Analysis Set
PPS	Per Protocol Analysis Set
PR	Partial Response
PT	Preferred Term
QTcF	QT interval with Fridericia's Correction
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOPs	Standard Operating Procedures
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
VR	Ventricular Rate
WBC	White Blood Cell
WHO	World Health Organisation

1 INTRODUCTION

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 two heavy chains of 451 amino acids each and two 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).

This document describes planned statistical analyses as well as the rules and conventions to be used in the presentation of efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity data for Dr. Reddy's Laboratories S.A.'s "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 Statistical Analysis Plan (SAP) is applicable for unblinded statistical analysis of all data up to Week 28, and for the statistical analysis of all data up to Week 52 after database lock and general unblinding after the end of the study.

For the purposes of analysis, the study will be unblinded to specified Sponsor/designee members (refer to the latest version of Blinding Maintenance Plan (BMP)) – but not investigators or subjects – once all subjects have reached Week 28 (or earlier termination of study). All individuals with access to unblinded data and analysis results up to Week 28 will sign a confidentiality agreement to maintain the study blind up to general unblinding after final database lock. For the Week 28 CSR analysis, all data up to Week 28 (±7 days, the allowed visit window for the Week 28 visit) will be included. Analysis for the Week 52 CSR will be prepared after database lock and general unblinding after study closure.

The analyses described in this SAP are based upon the following study documents:

- Clinical Study Protocol RI-01-006, version 5.0 (27 October 2021)
- Electronic Case Report Form (eCRF), Version 9.0 (21 March 2022).

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary objective is 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.

2.2 Secondary Objectives

Secondary objectives are:

- To compare overall response (OR) 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
- To compare safety, tolerability, and immunogenicity of DRL_RI with MabThera® in subjects with CD20-positive, LTB-FL

2.3 Exploratory Objectives

Exploratory objectives are:

- To compare BOR up to Week 28 evaluated in accordance with the Lugano criteria (Cheson 2014[4]) in subjects with CD20-positive, LTB-FL treated with either DRL_RI or MabThera®
- To explore the pharmacokinetic (PK) parameters of DRL_RI and MabThera®, using a population-PK modelling approach
- To explore the pharmacodynamic parameters of DRL_RI and MabThera®.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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

The study will enroll subjects with CD20-positive, LTB-FL who are asymptomatic for lymphoma specific B-symptoms. LTB-FL will be assessed according to the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria.[3]

Subjects will be randomized in a 1:1 ratio to one of the 2 study treatment groups:

- DRL_RI
- MabThera®

Randomization will be stratified by

- CCI [redacted] CCI [redacted], see Section 4.10.1.6): low risk versus medium risk versus high risk
- tumor grade: 1-2 versus 3a
- geographical regions: United States of America (USA) versus Europe versus Asia Pacific.

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 Body Surface Area (BSA), please see Section 4.7 for BSA formulas.

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 until Week 36, please see Figure 1 further below for study drug administration schedule.

Study will consist of:

- Screening: up to 35 days to assess & confirm study eligibility
- Treatment period: up to 36 weeks that includes both induction and maintenance periods. Subjects will attend study visits every week (± 2 days) during the Induction Treatment Period, Weeks 1 to 4 and at Week 8 (± 7 days). During maintenance treatment period subjects will attend the study visit at Week 12 ± 7 days, and thereafter every 8 weeks (±7 days) until Week 36.
- Follow-up Period: subjects will be followed 52 weeks after the first dose of study drug (at Weeks 44 and 52)

Study procedures include physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, tumor assessments, clinical laboratory tests, serum lactate dehydrogenase (LDH) and β-2 microglobulin, coronavirus disease 2019 (COVID-19) testing at screening

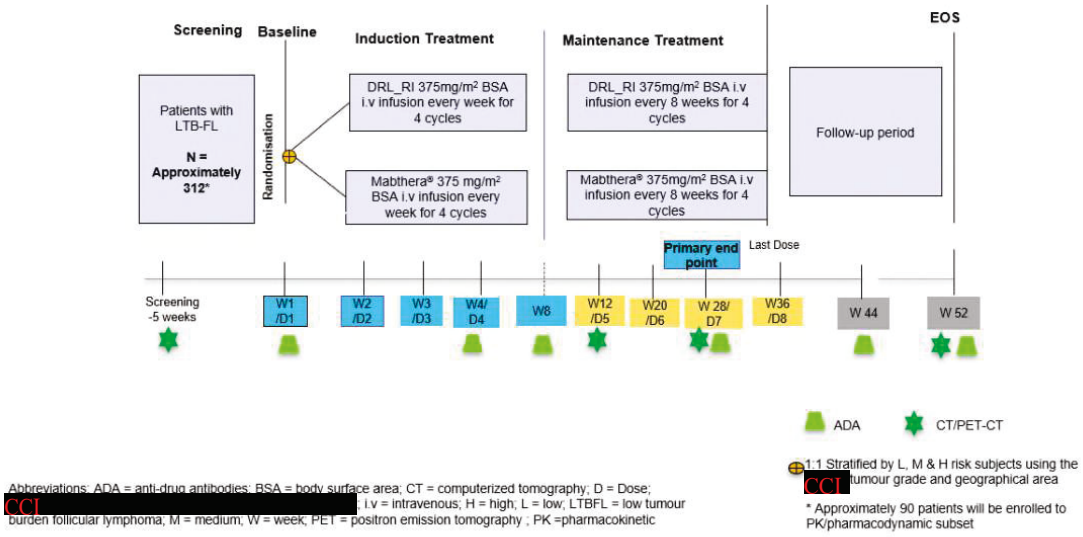
and as deemed appropriate by the Investigator at any time during the study, adverse events (AEs), concomitant medication, immunogenicity, and PK and pharmacodynamic samplings for the subjects in the corresponding subset.

Subjects completing the study at Week 52 will attend an EOS Visit. Subjects discontinuing the study before Week 52 for any reason will attend an ET Visit.

Figure 1 below illustrates the study design.

The study schedule details the procedures and tests occurring at specific times throughout the study and are listed in Appendix 1 Schedule of Assessments.

Figure 1 Overview of the study design



The Study will have a Data Monitoring Committee (DMC) to independently review blinded sample size re-estimation (BSSR) and for overall progress review of study. DMC data review meetings will occur at the milestones predefined at charter. All activities related to the DMC will be conducted by DRL. Parexel will only support for BSSR analysis and will provide raw data in medical listing format.

3.2 Definition of Endpoints / Variables

3.2.1 Definition of Efficacy Endpoints / Variables

3.2.1.1 Definition of the Primary Efficacy Endpoint / Variable

BOR up to Week 28 is defined as the best overall response at any radiologic tumor evaluations (based on central radiology review applying the Cheson 1999[2] response criteria for malignant lymphoma) up to the end of the allowed window for the Week 28 evaluations. Unscheduled and early termination evaluations will be only considered if they are complete and performed up to the end of the allowed window for the Week 28 evaluations.

The primary efficacy endpoint used in the statistical analysis is a binary (response / non-response) BOR up to Week 28 version is defined below. The impact of Intercurrent Events on binary BOR up to Week 28 is not described here but in Section 4.10.2.

For subjects with known tumor response at both Week 12 and Week 28, the definition of binary version of BOR up to Week 28 (the primary efficacy endpoint in the statistical analysis) is:

Response at Week 12	Response at Week 28	Binary version of BOR up to Week 28
CR, CRu or PR	Any known	Response
Any Known	CR, CRu or PR	Response
SD or PD	SD or PD	Non-Response

For subjects with a missing / unknown ("unknown" covers "not evaluable", "not available", "subject not anymore in the study", etc.) tumor response at Week 12 or at Week 28 and tumor response known at the other time-point, the definition of binary version of BOR up to Week 28 is:

Response at Week 12	Response at Week 28	Binary version of BOR up to Week 28
CR, CRu or PR	Missing / Unknown	Response
Missing / Unknown	CR, CRu or PR	Response
SD or PD	Missing / Unknown	Non-Response
Missing / Unknown	SD or PD	Non-Response

For subjects with only missing / unknown tumor responses, the definition of binary version of BOR up to Week 28 is:

Response at Week 12	Response at Week 28	Binary version of BOR up to Week 28
Missing / Unknown	Missing / Unknown	• Non-Response for main analysis using the exact score method, sensitivity analysis using stratified Mantel-Haenszel method, and FDA main estimand • Missing for sensitivity analyses within the estimand framework (except FDA main estimand) using multiple imputation approaches and for supplementary analyses as described in Section 4.10.2.3

3.2.1.2 Definition of Secondary Efficacy Endpoints / Variables

Secondary efficacy endpoints / variables are:

- Overall response (of either CR, CRu or PR) at Week 12 and overall response (of either CR, CRu or PR) at Week 28 based on central radiology review applying the Cheson 1999[2] response criteria for malignant lymphoma

- Complete Response (CR) at Week 28 based on central radiology review applying the Cheson 1999[2] response criteria for malignant lymphoma
- Complete Response (CR) as best response up to Week 28 (derivation similar to primary endpoint, BOR) based on central radiology review applying the Cheson 1999[2] response criteria for malignant lymphoma
- Duration of response (DOR) based on central radiology review applying the Cheson 1999[2] defined as time from date of the first documentation of tumor response (CR, CRu or PR) to date of first documentation of PD or to date of death due to any cause (whatever is first) up to Week 52 / EOS + 1
- Progression-free survival (PFS) by central review applying the Cheson 1999[2] progression criteria for malignant lymphoma is defined as the time from date of randomization to the date of documented PD (PD from imaging shared through central imaging data or eCRF early termination page) or death due to any cause up to Week 52 / EOS + 1. PFS censoring rules are defined in Section 4.10.3.1.
- Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause up to Week 52 / EOS + 1. OS censoring rules are defined in Section 4.10.3.5.

3.2.1.3 Definition of Exploratory Efficacy Endpoints / Variables

Exploratory efficacy endpoint / variable is:

BOR (CR or PR) up to Week 28 is defined as the best overall response at any radiologic tumor evaluations (based on central radiology review applying the Lugano criteria (Cheson 2014[4]) up to the end of the allowed window for the Week 28 evaluations for subjects with available positron emission tomography (PET) data. Unscheduled and early termination evaluations will be only considered if they are complete and performed up to the end of the allowed window for the Week 28 evaluations. The exploratory efficacy endpoint used in the statistical analysis is a binary (response / non-response) BOR up to Week 28 version as defined below.

For subjects with known tumor response at both Week 12 and Week 28, the definition of binary version of BOR up to Week 28 is:

Response at Week 12	Response at Week 28	Binary version of BOR up to Week 28
CR or PR	Any known	Response
Any Known	CR or PR	Response
SD or PD	SD or PD	Non-Response

For subjects with a missing / unknown ("unknown" covers "not evaluable", "not available", "subject not anymore in the study", etc.) tumor response at Week 12 or at Week 28 and tumor response known at the other time-point, the definition of binary version of BOR up to Week 28 is:

Response at Week 12	Response at Week 28	Binary version of BOR up to Week 28
CR or PR	Missing / Unknown	Response
Missing / Unknown	CR or PR	Response
SD or PD	Missing / Unknown	Non-Response
Missing / Unknown	SD or PD	Non-Response

3.2.2 Definition of Safety Endpoints / Variables

Safety endpoints / variables are:

- AEs and SAEs, as assessed by the US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0[8].
- Infusion reactions
- Vital signs
- Clinical safety laboratory tests (hematology, coagulation, biochemistry, urinalysis)
- 12-lead ECG
- ECOG performance status
- Physical examination
- Anti-rituximab antibodies and immunogenicity measures (BAb and Nab)

3.2.3 Definition of Other Endpoints / Variables

Other endpoints / variables are:

- Pharmacokinetic (PK) parameters (e.g., clearance and volume of distribution) for DRL_RI and MabThera® derived by a population PK modelling approach (not covered by this SAP)
- Pharmacodynamic variables:
  - Emax: maximum post-dose depletion of B-cell counts, calculated as the maximum of the B-cell depletion-time curve defined as baseline (pre-dose at Visit 1) count minus post-baseline count
  - AUEC: area under the B-cell depletion-time curve up to the last value below or equal to the subject's baseline count prior to the subject's first count above the subject's baseline count (if there is any such value above the subject's baseline count)
  - Time to first B-cell depletion: time from date of randomization to the first occurrence of a value below the lower limit of quantification (for subjects with a baseline B-cell count below the lower limit of quantification, this endpoint is not defined)
  - Time to first B-cell repletion: time from the date of the first B-cell depletion (as defined above) to the subsequently first occurrence of a value above or equal to the lower limit of quantification (for subjects without a B-cell depletion, this endpoint is not defined).

4 STATISTICAL METHODS

4.1 Quality Control

All tables, figures and listings planned in this SAP will undergo quality control in accordance with Parexel's Standard Operating Procedures (SOPs).

4.2 General Presentation Considerations

4.2.1 General Continuous Data Presentation

Continuous data will be summarized in terms of the mean, standard deviation (SD), coefficient of variation as appropriate, median, minimum, maximum and number of non-missing observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations.

Minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. Mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

4.2.2 General Categorical Data Presentation

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will be calculated using 'n' (the total number of subjects providing data at the relevant time point) as the denominator.

4.2.3 Study Day and Study Week

Study Day (in days) will be calculated from date of randomization, and it will be used to show start and stop day of assessments or events.

For visit (or event) prior to randomization,

Study day = Date of assessment (or event) – (Date of randomization).

For visit (or event) at or after randomization,

Study day = Date of assessment (or event) – (Date of randomization) + 1.

In case that the event date is partial or missing, the date will appear partial or missing in the listings. Study day will be calculated after imputation has been carried out as described in Appendix 2 Partial Date Conventions.

4.2.4 Baseline Measurements

For efficacy analyses, the baseline value is defined as the last non-missing measurement value prior to the randomization.

For safety analyses, the baseline value is defined as the last non-missing measurement collected on or before first study drug administration. However, if there is evidence that measurements are taken on the same day as administration of first IP, then a value taken strictly prior to the time of study drug administration or previous day(s) (closest to first study drug administration) will be used as baseline value.

4.2.5 Treatment periods

Treatment periods are defined as:

- Induction Treatment Period (Week 1 to Week 4): (End date of Week 4 - Start date of Week 1) +1
- Maintenance Treatment Period (Week 12 to Week 36): (End date of last available visit in maintenance period /Week 36 - Start date of Week 12) +1, data as available for the subject who are still in the study.

4.2.6 Visit windowing

Nominal Visit will be used as collected in eCRF pages, except for vital signs. No visit window will be applied for other safety assessments. Study visits will be labelled as Screening, Induction Period- Baseline (Day 0), Week 2 (Day 8), Week 3 (Day 15), Week 4 (Day 22), Week 8, maintenance Period- Week 12, 20, 28 and 36, Follow-up period- Week 44, Week 52 (EOS/ET). For the subjects who prematurely discontinue the study prior to Week 52, their EOS/ET visit will be mapped to the correct visit based on target day.

Unscheduled Visits and Multiple Assessments

In general, unscheduled and retest (except for vital signs assessment) safety measurements will not be included in the by-visit summaries. Listings will include all scheduled, unscheduled, retest and early discontinuation data with the nominal visit originally recorded on the eCRF.

For vital signs since the assessments are being collected at every 30 minutes (±5 minutes) during the course of the treatment administration and at end of infusion or more frequently as necessary, the summaries will be provided for each of timepoint available with in a visit for all the subjects. Difference between infusion start date/time to vital sign assessment date/time will be calculated and duration will be rounded to 0 min, 30 min, 60 min, etc. It is possible that multiple assessments of a subjects fall into the same visit-window of a timepoint, then the assessment closest to the target timepoint will be selected and rounded.

For tables displaying the worst-case scenario, such as shift tables or notable abnormalities, all assessments including unscheduled assessment will be used to identify the worst (e.g. the maximum or the minimum depending on parameter). Where applicable it will be defined for each parameter what the worst case is.

[redacted]

CCI [redacted]

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

	CCI [redacted]	CCI [redacted]

4.2.8 Common Calculations

For quantitative measurements, changes from baseline at Visit will be calculated as follows:

- Change at Visit = Measurement value at Visit – Baseline Value (Baseline)
- Changes from baseline in categorical data will be summarized using shift tables, where appropriate.

Durations (excluding treatment duration) are calculated as:

- Duration (days) = End Date – Start Date + 1
- Duration (weeks) = (End Date – Start Date + 1) / 7
- Duration (months) = (End Date – Start Date + 1) / 30.44.

4.2.9 Other Considerations

In general, listings will be sorted and presented by treatment group and subject number across all sites.

Confidence intervals (CIs), two-sided 95% for EMA and two-sided 90% for FDA, will be presented to one more decimal place than the raw data.

4.3 Software

All tables, figures and listings for Clinical Study Report (CSR) will be produced using SAS® version 9.4 (or a later version) in a secure and validated statistical computing environment. The version of SAS® actually used for the analysis will be noted in the CSR.

4.4 Analysis Sets

4.4.1 Intention-To-Treat Analysis Set

The Intention-To-Treat (ITT) Analysis Set will include all randomized subjects. The primary efficacy analysis will be based on the ITT Analysis Set.

If a subject received incorrect study drug, i.e., study drug different to the one assigned per the randomization list, the subject will be summarized and analyzed for the study treatment group per the randomization list. If a subject's stratum has been entered incorrectly in the randomization system, i.e., conflicting with the data in the clinical database, the stratum entered in the randomization system will be used for summaries and analyses.

4.4.2 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPS) will include all randomized subjects who

- received at least one dose of study drug (sufficient compliance as defined in Section 4.9)
- have measurable disease at Baseline as confirmed by central review
- have an at least one available valid response evaluation up to Week 28 (± 4 weeks)
- and no major protocol deviations (such as administration of a forbidden treatment) that would significantly impact the primary efficacy endpoint (if, however, the forbidden treatment was administered due to PD, the subject will be included in the PPS as a non-responder).

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 ± 4 weeks of the scheduled date, and the central imaging reviewers consider all imaging at Week 12 and 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.

Final composition of the PPS will be determined prior to unblinding.

4.4.3 Safety Analysis Set

The Safety Analysis Set (SAF) will include all subjects who have received at least one dose of study drug. The SAF will be used for safety analysis.

If a subject received incorrect study drug, i.e., study drug different to the one assigned per the randomization list, the subject will be summarized and analyzed for the study drug actually received.

4.4.4 Pharmacokinetic Analysis Set

The PK Analysis Set (PKS) will include all randomized 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 are included in the PK and pharmacodynamic subset if they consented and participated in the PK and pharmacodynamic evaluations.

4.4.5 Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set (PDS) 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 are included in the PK and pharmacodynamic subset if they consented and participated in the PK and pharmacodynamic evaluations.

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

4.4.6 Immunogenicity Analysis Set

All randomized subjects with at least one immunogenicity sample with a valid result will be included in the Immunogenicity Analysis Set.

4.4.7 eCRF CCI Risk Category Analysis Set

The eCRF CCI Risk Category Analysis Set will include all subjects from the ITT Analysis Set but with study treatment received (even if different from the randomized study treatment) and CCI risk category as per eCRF (even if different from the category used in the stratified randomization).

4.4.8 eCRF Tumor Grade Analysis Set

The eCRF Tumor Grade Analysis Set will include all subjects from the ITT Analysis Set but with study treatment received (even if different from the randomized study treatment) and tumor grade as per eCRF (even if different from the category used in the stratified randomization).

4.4.9 Analysis Set Summaries

Analysis sets will be summarized and listed for the ITT Analysis Set by:

- Summary of number and percentage of subjects in the respective analysis set, by treatment group and overall

- By-subject listing including treatment group, center, subject identifier, inclusion/exclusion flag for each analysis set and reason for exclusion from an analysis set, if applicable.

4.5 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the subject's rights, safety, well-being, and/or the primary efficacy endpoint BOR up to Week 28.

Subjects with major protocol deviations (defined below) will be excluded from the PPS. Please refer to the study protocol deviation specification for more information.

A summary of the number and percentage of subjects with protocol deviations by protocol deviations classification (minor or major), will be provided by treatment group for the ITT Analysis Set. Protocol deviations related to the COVID-19 pandemic will be summarized for the ITT Analysis Set.

A by-subject listing will be provided including subject identifier, protocol deviation classification, protocol deviation description and exclusion from specific analysis sets. Protocol deviations related to the COVID-19 pandemic will be presented in a separate listing.

4.6 Study Subjects

4.6.1 Disposition of Subjects

The disposition of all subjects who enter the study will be provided, from enrolment to study completion. The subject disposition summaries include the following (overall and by treatment group where applicable) summaries based on associated analysis sets:

4.6.1.1 Subjects Screened

A summary of the number of subjects screened with the number and percentage of screen failures and reasons for screen failure.

4.6.1.2 Subjects Randomized

A summary of number of subjects who satisfied eligibility criteria for enrolment and were randomized to one of the two study treatment groups.

4.6.1.3 Subjects Treated

The number of subjects who received treatment, completed Week 12, Week 28, completed study and discontinued from study along with primary reason of discontinuation from study will be summarized and listed.

The similar summary for subject disposition will be performed by stratification factors: CCI risk category, tumor grade, geographical area as well as by, treatment group and overall.

A separate summary of subject's disposition by treatment period will also be provided. This display will show the number of subjects who initiated induction treatment, completed induction treatment period, completed induction period and started maintenance treatment period, who initiated maintenance treatment, completed maintenance treatment period, entered follow up, completed follow-up, and who discontinued from induction/ between induction period completion and starting of maintenance treatment period /maintenance treatment/, the primary reasons of discontinuation including disease progression, adverse events, death, subject withdrew consent, lost to follow-up, investigator's decision, COVID-19 or related symptoms and other reasons will be summarized by treatment group and overall.

4.6.1.4 Subjects per Analysis Set

A summary of the number of subjects per analysis set will be provided (see Section 4.4 for definition of analysis sets).

A by-subject listing of subject disposition will be generated that includes start/end date of screening, randomization, screening failure date, reason of screening failure, subject's received treatment, completion / early termination of treatment date, completion of study / early termination of study date, along with primary reason for early termination. A separate listing of subject disposition will be provided which includes induction treatment, maintenance treatment and follow-up along with primary reasons for early termination, if any.

4.7 Demographic and Other Baseline Characteristics

All demographic summaries will be produced for the ITT Analysis Set.

Demographic and baseline characteristics (see Sections 4.7.1 and 4.7.2) measured before randomization will be listed by subject and summarized by treatment group and overall, for the ITT Analysis Set.

4.7.1 Demographics Characteristics

- Age (years)
- Age group: < 60, ≥ 60 years
- Gender: Male, Female
- Height and weight as per IVRS
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, White, Black, Asian, Multiracial, Native, Not Reported, Unknown
- Race: White, Asian, Black or African American, American Indian or Alaska Native, Aboriginal/Torres Strait Islander, Native Hawaiian or Other Pacific Islander, Unknown, Not reported, Other
- BSA(m^2) as per eCRF.
- Geographical Region: USA, Europe, Asia Pacific.

Note: BSA may be calculated by any of the below derivation methods.

Mosteller[5] formula:

$$\text{BSA}[m^2] = \sqrt{\frac{\text{Height}[cm] \times \text{Weight}[kg]}{3600}}$$

Du Bois[6] formula:

$$\text{BSA}[m^2] = 0.007184 \times \text{Height}[cm]^{0.725} \times \text{Weight}[kg]^{0.425}$$

Haycock[7] formula:

$$\text{BSA}[m^2] = \text{Weight}[kg]^{0.5378} \times \text{Height}[cm]^{0.3964} \times 0.024265.$$

4.7.2 Other Baseline Characteristics

Other baseline characteristics are:

- Eastern cooperative oncology group (ECOG) performance status: 0, 1, ≥ 2

- Serum beta-2 microglobulin: normal, above upper limit of normal
- Hemoglobin level: ≥120 g/L, <120 g/L
- Bone marrow involvement: absent, present
- CCI [redacted]
- Histological Tumor Grade for FL: grade 1, grade 2, grade 3a
- Histological Tumor Grade for FL as per randomization stratum: grade 1 or 2, grade 3a.

4.7.3 Social and Economic Factors

Baseline social and economic factors will be listed. These factors include educational qualification, occupation, income, family history of allergy related to cancer, alcohol ever consumed, amount of beer consumed, frequency of beer consumed, amount of wine consumed, frequency of wine consumed, amount of spirits consumed, frequency of spirit consumed, any drug abuse, drug usage, and frequency of drug usage.

The by-subject listings will also include additional information provided for these factors such as amount of beer consumed, start of date of drug usage etc.

4.7.4 Follicular Lymphoma Staging

Follicular lymphoma staging will be listed by subject and summarized by treatment group and overall. The number and percentage of subjects will be provided for the following:

- Disease diagnosis histologically confirmed,
- Ann Arbor staging
- CCI [redacted]

The by-subject listings will also include additional information provided for these factors such as date of histological conformation etc.

4.7.5 Disease Diagnosis

Disease diagnosis will be listed by subject and summarized by treatment group and overall. The number and percentage of subjects will be provided for: Time since initial diagnosis, time since histological confirmation, scan type/modality, CD20 positivity confirmation, current site of disease, disease confirmation by bone marrow biopsy, histological confirmation, any prior anti-cancer therapy, any surgery related to current cancer and any prior radiotherapy for current cancer.

In addition to above, the by-subject listings will also include date of initial diagnosis, scan type/modality, date of biopsy and date of histological confirmation.

4.7.6 Medical and Surgical History including medications

Medical conditions will be coded by the Medical Dictionary for Regulatory Activities (MedDRA). The final MedDRA version to be used will be decided prior to database lock (for both primary and final analysis).

Medical and surgical history/conditions present at screening will be summarized and listed. They will be summarized by MedDRA primary System Organ Class (SOC) and Preferred Term (PT). Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the condition was ongoing at the time of first study drug administration. The number and percentage of subjects with each medical condition will be provided by treatment group for the SAF.

4.8 Prior and Current Concomitant Medication

All medications taken by a subject within one month prior to screening are regarded as prior medications 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 medications and must be documented as such in the eCRF. Imputation of partial dates for prior and concomitant medication is described in Appendix 2 Partial Date Conventions.

A summary of the number of subjects with prior and current concomitant medications by treatment group and overall will be generated for the SAF. The number (n) and percentage will be provided by Anatomical Therapeutic Chemistry (ATC) term, PT by World Health Organization - Drug Dictionary Enhanced (WHO-DDE) version SEP2020 B3 and each subject will be counted once only under each category. A similar summary table for prior and current concomitant medications taken due to COVID-19 for the SAF will also be presented.

A by-subject listing of prior/current concomitant medication will be generated using the SAF, including start/end date of medication taken, dose information (dose name, unit, total dose, route and frequency), indication /reason for treatments, and any anti-cancer therapies/ radiotherapies/ surgeries taken during the study. Prior and concomitant medications taken due to COVID-19 will be presented in a separate listing.

4.9 Treatment Compliance

Study treatment compliance will be calculated as follows and will be summarized for the SAF:

$$\text{study treatment compliance}(\%) = \frac{\text{total dose administered (mg)}}{\text{total intended dose (mg)}} \times 100$$

For subjects with early study treatment discontinuation, dose intended and administered, respectively, up to the study treatment discontinuation will be considered for compliance calculation.

A summary of treatment compliance by treatment group and visit (including the number and percentage of compliant and non-compliant subjects) will be provided for induction period and maintenance period. Compliant subjects are those subjects who had 95% to 105% study treatment compliance, otherwise subjects will be considered non-compliant.

A by-subject listing of study drug infusion including starting and end date and time, visit, intended dose, actual dose administered, volume administered, body surface area, dose delay, missed dose, reason for interruption or discontinuation, rate of infusion, duration of infusion, reason for interruption or discontinuation during infusion, kit allocation date, kit number and AE details that lead to interruption or discontinuation will also be provided.

4.10 Efficacy Analyses

4.10.1 Analysis and Data Conventions

4.10.1.1 Multi-center Studies

For the following sections of safety and efficacy analysis, the term 'Center' in this SAP will be defined as investigator site.

Data from participating centers will be pooled prior to analysis. However, summary of randomized subjects by geographical region and investigator sites (if available) will be provided.

4.10.1.2 Adjustments for Covariates

No covariate adjustment is planned in the primary efficacy endpoint main analysis.

Stratification variables used in the stratified randomization will be included in stratified analyses of the primary efficacy endpoint as a part of sensitivity analysis.

4.10.1.3 Handling of Missing Data

Various approaches will be applied to handle missing data; main, sensitivity and supportive analyses will be performed to explore the robustness of statistical results for the primary efficacy endpoint, see Sections 4.10.2.2.3 to 4.10.2.3.

Analysis and descriptive summaries for other endpoints will be based on available observed data.

4.10.1.4 Multiple Comparisons/Multiplicity

No multiplicity adjustment is needed for this study as there is only one primary efficacy endpoint, no repeated analysis of the primary endpoint and each Health Authority will base the statistical analysis of the primary endpoint on either the FDA or EMA approach described in this SAP.

4.10.1.5 Interim Analyses

Not applicable.

4.10.1.6 Examination of Subgroups

Subgroup analyses will be performed for the ITT Analysis Set to examine primary efficacy endpoint BOR up to Week 28 by CCI index, tumor grade, geographical region, gender, age group (< 60, ≥ 60 years), race, Ann Arbor stage, bone marrow involvement at baseline (Present, Absent) and baseline serum LDH concentration at baseline (Low/Normal, High). Difference in BOR up to Week 28 probabilities along with 90% and 95% CI will be performed using the unstratified exact score method by Chan 1999[9] by subgroups will be presented in forest plots.

A summary of AE infusion related reaction (IRR) will be provided for subgroups CCI, tumor grade and geographical region. For details refer to Section 4.11.2.

4.10.2 Analysis of the Primary Efficacy Endpoint / Variable

4.10.2.1 Main Analysis of the Primary Efficacy Endpoint / Variable

The main analysis will be performed for the ITT Analysis Set and the primary efficacy endpoint / variable (BOR up to Week 28) is defined in Section 3.2.1.1 (with non-response for subjects without any valid post-baseline tumor assessment up to Week 28).

Statistical hypotheses

With

$\pi_{\text{DRL\_RI}}$ denoting the true probability for BOR up to Week 28 in the DRL_RI treatment group

$\pi_{\text{MabThera®}}$ denoting the true probability for BOR up to Week 28 in the MabThera® treatment group

and $\delta = \pi_{\text{DRL\_RI}} - \pi_{\text{MabThera®}}$ denoting the BOR up to Week 28 probability difference,

the null hypothesis is

H_0: $|\delta| \geq 0.17$,

verbally: DRL_RI is not biosimilar (is either inferior or superior) to MabThera® applying pre-specified symmetrical biosimilar margins ±0.17 (±17%).

The alternative hypothesis is

H_A: $|\delta| < 0.17$,

verbally: DRL_RI is biosimilar (is neither inferior nor superior) to MabThera® applying pre-specified symmetrical biosimilar margins ±0.17 (±17%).

Statistical analysis method

Two-sided 90% and 95% CIs for the BOR up to Week 28 probability difference ((DRL_RI minus MabThera®) will be obtained by the unstratified exact score method (Chan 1999[9]) implemented in SAS Proc FREQ.

For FDA, biosimilarity will be concluded (i.e., the null hypothesis rejected) if the 90% CI is completely contained within the pre-defined interval (-0.17, 0.17).

For EMA, biosimilarity will be concluded (i.e., the null hypothesis rejected) if the 95% CI is completely contained within the pre-defined interval (-0.17, 0.17).

4.10.2.2 Sensitivity Analyses of the Primary Efficacy Endpoint / Variable

4.10.2.2.1 Stratified Analysis for Primary Efficacy Endpoint / Variable

Statistical Hypotheses

For the stratified analyses, the hypotheses will be as follow:

With

$\pi_{\text{DRL\_RI,j}}$ denoting the true probability for BOR up to Week 28 in the DRL_RI treatment group in stratum j, $1 \leq j \leq 18$ (for the 18 strata used in the stratified randomization)

$\pi_{\text{MabThera®,j}}$ denoting the true probability for BOR up to Week 28 in the MabThera® treatment group in stratum j, $1 \leq j \leq 18$ (for the 18 strata used in the stratified randomization)

and $\delta = \pi_{\text{DRL\_RI,j}} - \pi_{\text{MabThera®,j}}$ denoting the common BOR up to Week 28 probability difference (common across the 18 strata used in the stratified randomization),

the null hypothesis is

H_0: $|\delta| \geq 0.17$,

verbally: DRL_RI is not biosimilar (is either inferior or superior) to MabThera® applying pre-specified symmetrical biosimilar margins ±0.17 (±17%).

The alternative hypothesis is

H_A: $|\delta| < 0.17$,

verbally: DRL_RI is biosimilar (is neither inferior nor superior) to MabThera® applying pre-specified symmetrical biosimilar margins ±0.17 (±17%).

Statistical analysis method

Two-sided 90% and 95% CIs for the BOR up to Week 28 common probability difference between treatment groups (DRL_RI minus MabThera®) will be obtained using the stratified Mantel-Haenszel method[10,11], stratified by the strata used in the stratified randomization and implemented in SAS Proc FREQ. This analysis will be performed for the ITT analysis set.

4.10.2.2.2 Intercurrent Events

Table 1 and Table 2 lists the intercurrent events (ICEs) identified as relevant for BOR up to Week 28 for FDA and EMA respectively.

Table 1 Intercurrent Events for FDA

Intercurrent Event for FDA
Death prior to first post-baseline radiologic tumor examination
Missing scheduled post-baseline radiologic tumor examination up to Week 28 (for reason other than death) • reason not related to COVID-19 pandemic • reason related to COVID-19 pandemic
Initiation of forbidden treatment for LTB-FL prior to Week 28 radiologic tumor examination

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. The relevant eCRF data will be reviewed by medical experts to identify forbidden treatments per the above definition. The programming team will use that information to derive the forbidden treatment ICE.

Table 2 Intercurrent Events for EMA

Intercurrent Event for EMA
Death prior to first post-baseline radiologic tumor examination • reason for death known to be other than progressive disease • reason for death progressive disease or unknown
Discontinuation of study treatment prior to first post-baseline radiologic tumor examination • reason not related to COVID-19 pandemic • reason related to COVID-19 pandemic

Intercurrent Event for EMA
Missed or delayed study drug administration prior to Week 28 radiologic tumor examination • reason not related to COVID-19 pandemic • reason related to COVID-19 pandemic
Missing scheduled post-baseline radiologic tumor examination up to Week 28 (for reason other than death) • reason not related to COVID-19 pandemic • reason related to COVID-19 pandemic
Initiation of forbidden treatment for LTB-FL prior to Week 28 radiologic tumor examination

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. The relevant eCRF data will be reviewed by medical experts to identify forbidden treatments per the above definition. The programming team will use that information to derive the forbidden treatment ICE.

4.10.2.2.3 Main and Sensitivity Estimands

Table 3 describes main and sensitivity estimands for the FDA.

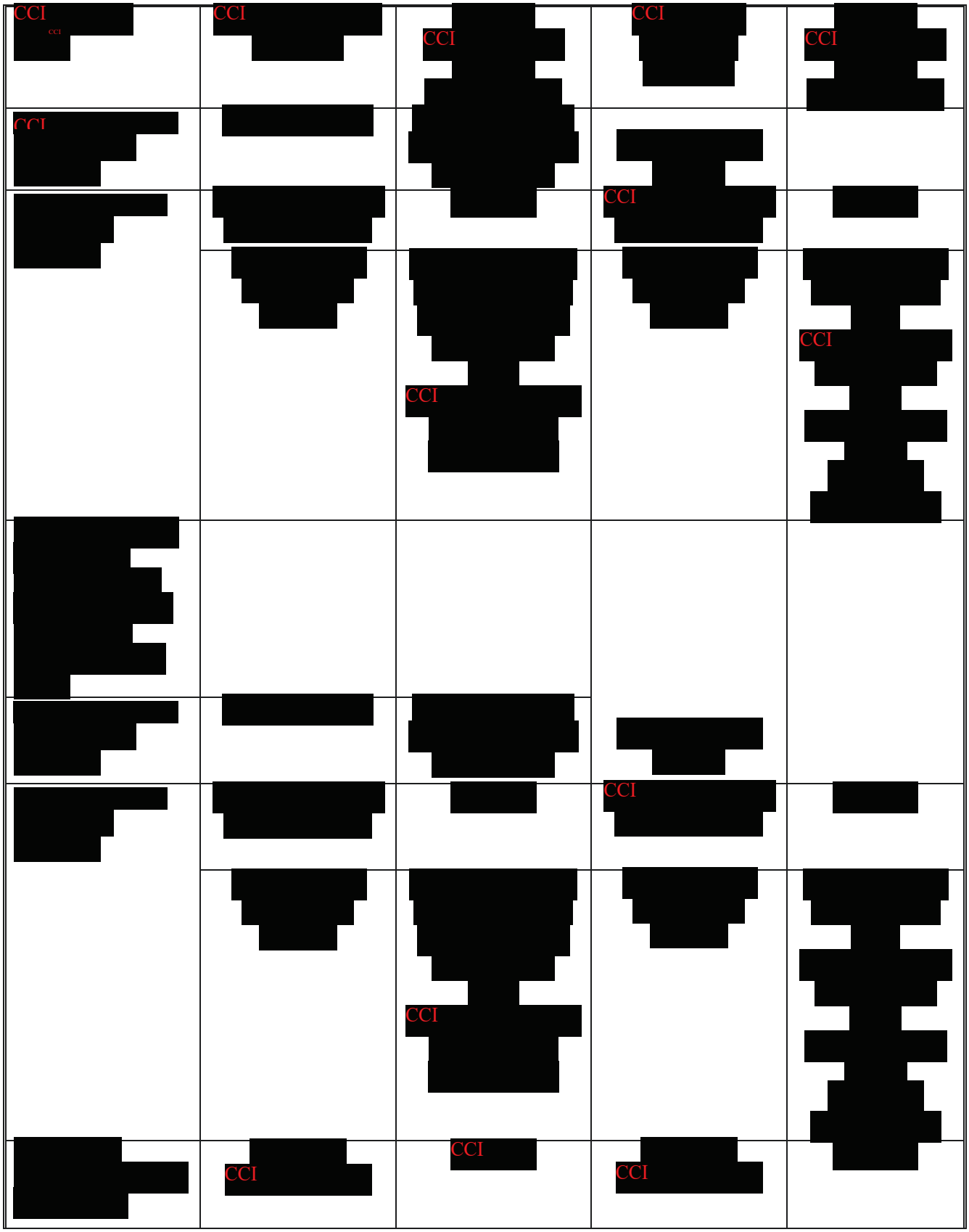
Table 3 Main and Sensitivity Estimands for FDA

Treatment conditions of interest	DRL_RI and MabThera®
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI	CCI
CCI				
• CCI	CCI	CCI	CCI	CCI
• CCI	CCI	CCI	CCI	CCI

Table 4 describes main and sensitivity estimands for the EMA.

Table 4 Main and Sensitivity Estimands for EMA

	DRL_RI and MabThera®



4.10.2.2.4 Statistical Hypotheses

$\pi_{\text{DRL\_RI,i}}$

$\pi_{\text{MabThera®,i}}$

$\delta = \pi_{\text{DRL\_RI,i}} - \pi_{\text{MabThera®,i}}$

$H_0: |\delta| \geq 0.17$

$H_A: |\delta| < 0.17$

[redacted]
CCI [redacted]

Statistical analysis method

For the final resulting dataset, SAS Proc FREQ will be used to obtain the point estimate and its standard error for BOR up to Week 28 common probability difference (using the stratified Mantel-Haenszel method[10,11], stratified by the strata used in the stratified randomization) between treatment groups.

Finally, the two-sided 90% CI for BOR up to Week 28 common probability difference reflecting the strategies for handling ICEs in the main estimand for FDA will be obtained and compared to the bio similarity margins for either rejecting or accepting the null hypothesis.

4.10.2.2.6 Analysis of Main Estimand for EMA

[redacted]
CCI [redacted]
[redacted]
.

MI prediction and imputation steps assuming MAR

CCI

Table 5 MI Prediction Model Assuming MAR

	CCI

CCI

[redacted]

CCI

MI prediction and imputation steps with specific MNAR rules

[redacted]

CCI

[redacted]

Table 6 MI Prediction Model with MNAR for Main Estimand for EMA

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

CCI	
	CCI

CCI

[redacted]
CCI
CCI CCI
CCI
CCI
CCI
$\bar{B}$
CCI
CCI
CCI CCI
CCI
o
CCI
CCI

Table 7 MI Prediction Model Assuming MAR for FDA

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

CCI
[redacted]

Table 8 MI Prediction Model with MNAR for Sensitivity Estimand for FDA

CCI [redacted]	[redacted]
Baseline	• Randomized study treatment (DRL_RI, MabThera®) • CCI [redacted] CCI [redacted]
[redacted]	[redacted] CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted] $m = 625$ [redacted] $t_{0.95,DF_{MI}}$ [redacted]

CCI [redacted]

4.10.2.2.8 Analysis of Sensitivity Estimand for EMA

CCI [redacted]

CCI [redacted]

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

Timepoint	Variables
	CCI [redacted]

4.10.2.3 Supplementary Analyses of the Primary Efficacy Endpoint / Variable

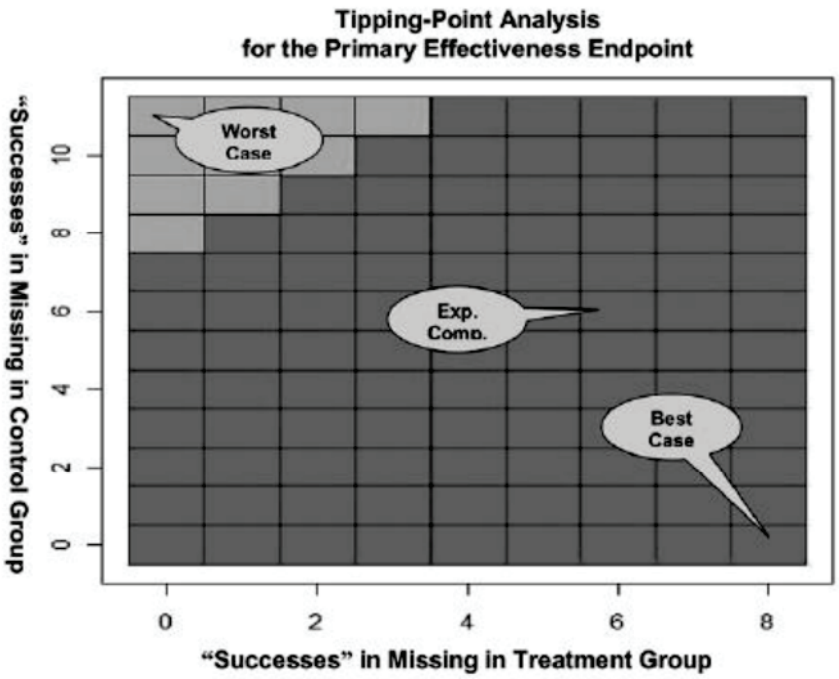
Supplementary analyses will be performed to further explore the robustness of statistical results for the primary efficacy endpoint.

4.10.2.3.1 Tipping point analysis

Graphical displays, based on the "tipping-point" analysis introduced by Yan 2009[12] and not requiring the MAR assumption, will be used to visualize the results of a two-dimensional set of sensitivity analyses using different imputations (either "response" or "non-response") for missing binary BOR up to Week 28 (per derivation in Section 3.2.1.1) values for comparison of the two treatment groups. All possible combinations of imputations of missing binary primary endpoint values in the DRL-RI and MabThera® treatment groups will be evaluated by the statistical method described in Section 4.10.2.1.

Figure 2 below displays a generic example with 8 missing binary endpoint values in the "Treatment Group" (one can impute 0 to 8 successes) and 11 missing binary endpoint values in the "Control group" (one can impute 0 to 11 successes), leading to a matrix of 108 (= 9 times 12) combinations to be tested. For the example displayed in Figure 2, 10 combinations close to the upper left upper corner "worst case" (all missing values in the "Control Group" were imputed as successes and all missing value in the "Treatment Group" were imputed as failures) did not lead to a significant test result (rejection of the null hypothesis).

Figure 2 Example for a Tipping Point Analysis Summary Display



"Enhanced tipping-point displays" (Liublinska 2014[13]) will be provided as compact summaries of conclusions drawn from different alternative assumptions.

4.10.2.3.2 Analyses using the PPS

The analyses described in Section 4.10.2.1 and Section 4.10.2.2.1 will be performed for the PPS (instead of the ITT Analysis Set).

4.10.2.3.3 Analysis using mixed multiple imputation for missing responses

Subjects considered non-evaluable due to administration of forbidden medications, or other treatments for LTB-FL will be considered non-responders and subjects considered non-evaluable due to any other reason will be imputed using the 0.058 overall response probability at Week 28 estimated in the watch and wait arm of a published randomized clinical study[9] which evaluated this treatment approach as compared to rituximab single agent. This supplementary analysis will be performed for the ITT Analysis Set. Both 90% and 95% CI will be calculated for the common BOR up to Week 28 probability difference.

Situations where missing BOR up to Week 28 will either be set to non-response or imputed for this supplementary analysis are given in Table 10 .

Table 10 Missing Response Types and Related Decisions

Missing response type	Decision on missing response
Subjects considered non-evaluable due to administration of forbidden medications, or other treatments for LTB-FL	Non-response
Subjects non-evaluable due to any other reason than the reasons stated above (administration of forbidden medication or any other treatment for LBT-FL)	Impute using 5.8% response rate

The algorithm for this supplementary analysis is described below-

Step 1: Let n_{1m} and n_{2m} be the number of subjects with missing responses in DRL_RI and MabThera® treatment groups

Step 2: Generate data X_{1m} from Bin(n_{1m},0.058) for DRL_RI treatment group, X_{2m} from Bin(n_{2m},0.058) for MabThera® treatment group

Step 3: Simulate m=1000 of such trials in step 2

Step 4: Conduct analysis as described in the MI part of Section 4.10.2.2.6

Step 5: Compare the resulting 90% and 95% CIs to (-0.17, 0.17).

4.10.2.3.4 Analysis with imputation under a non-inferiority assumption

For non-evaluable subjects in the DRL_RI treatment group, BOR up to Week 28 will be randomly imputed using a response probability of 0.71, whereas a response probability of 0.88 will be used for non-evaluable subjects in the MabThera® treatment group. The expected reference group response rate of 88.0% minus the non-inferiority margin of 17%. This supportive analysis will be performed for the ITT Analysis Set. Both 90% and 95% CI will be calculated for the common BOR up to Week 28 probability difference.

The algorithm for the above sensitivity analysis is described below-

Step 1: Let n_{1m} and n_{2m} be the number of subjects with missing responses in DRL_RI and MabThera® groups

Step 2: Generate data x_{1m} from Bin (n_{1m} , 0.71) for the DRL_RI treatment group and x_{xm} from Bin (n_{2m}, 0.88) for the Mabthera® treatment group

Step 3: Simulate m=1000 of such trials in step 2

Step 4: Conduct analysis similar as described in the MI part of Section 4.10.2.2.6

Step 5: Calculate CIs for this combined estimate and see if CI are within (-0.17, 0.17)

4.10.2.3.5 Analysis using study treatment received and stratification data as per eCRF

This supplementary analysis attempt to explore the impact of mis-stratification in the randomization process: same analysis (but now for the eCRF CCI Risk Category Analysis Set and the eCRF Tumor Grade Analysis Set) as for main estimands for FDA and EMA and also for sensitivity analysis will be performed but the analysis steps in those sections 4.10.2.2.1,4.10.2.2.5 and 4.10.2.2.6 will be stratified using strata data per eCRF (instead of per IWRS) and using study treatment received (instead of study treatment as randomized).

4.10.3 Analysis of Secondary Efficacy Endpoints / Variables

Definitions of secondary efficacy endpoints / variables are found in Section 3.2.1.2; they will be analyzed for the ITT Analysis Set.

4.10.3.1 Analysis of Progression Free Survival by Central Review

PFS (see Section 3.2.1.2) by central review will be summarized descriptively and graphically using Kaplan Meier methods. The Kaplan Meier 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 summarized by treatment group. If data warrant, the Kaplan-Meier estimate for the median progression free survival time and the first and third quartiles will be determined along with 95% CIs using the Brookmeyer-Crowley method. For the analysis of PFS, the PD assessment by central review will be used to determine the status and date of events for PFS regardless of treatment discontinuation.

A by-subject listing will be provided for central review as well as investigator assessed PFS by treatment group.

Table 11 provides the detailed event/censoring rules for statistical analysis of PFS.

Table 11 Event/Censoring Rules for PFS Analysis

Situation	Date	Outcome
No baseline tumor assessment	Date of randomization	Censored
PD or death at or before next scheduled assessment	Date of the first radiological tumor assessment demonstrating PD, or date of death	Progressed
New anticancer treatment started without documented PD	Date of last radiological tumor assessment prior to initiation of new therapy	Censored
PD or death after more than one missing assessments	Date of the last radiological tumor assessment prior to the missing assessments	Censored
No PD and no death	Date of the last radiological tumor assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

For the Week 28 CSR analysis, subjects will be administratively censored at Week 28 if no progression or other censoring appeared prior to Week 28.

4.10.3.2 Analysis of Overall Response by Central Review at Week 12 and at Week 28

OR by central review at Week 12 and at Week 28 will be summarized using frequencies, percentages and corresponding 95% CIs by treatment group.

4.10.3.3 Analysis of Complete Response by Central Review at Week 28

Complete response (CR) by central review at Week 28 will be summarized using frequency, percentage and corresponding 95% CI by treatment group.

4.10.3.4 Analysis of Complete Response by Central Review up to Week 28

Complete response (CR) by central review up to Week 28 will be summarized by using frequency, percentage and corresponding 95% CI by treatment group.

4.10.3.5 Analysis of Overall Survival

OS will be summarized descriptively and graphically using Kaplan Meier methods. The Kaplan Meier 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 summarized by treatment group. If data warrant, the Kaplan-Meier estimate for the median overall survival time and the first and third quartiles will be determined along with 95% CIs using the Brookmeyer-Crowley method.

A by-subject listing will be provided for OS by treatment group.

If a subject is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact. For example, if information of death is still pending or unknown under clinical operation and could not be obtained this information during the dry run analysis, then the last contact date will be considered as censored date of overall survival analysis. For the Week 28 CSR analysis, subjects will be administratively censored at Week 28 if no death or other censoring appeared prior to Week 28.

4.10.3.6 Analysis of Duration of Response by Central Review

Duration of response (DOR) by central review is defined as the time from date of the first documentation of tumor 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. Subjects continuing without PD or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the event/censoring rules described for PFS analysis, see Table 11. For the Week 28 CSR analysis, DOR data until a cutoff date not earlier than the date of the latest Week 28 evaluation conducted for any study subject will be included in the analysis. Additionally, DOR data will also be summarized for all subjects based on their Week 28 visit cut date.

DOR will be summarized descriptively and graphically using Kaplan Meier methods. The Kaplan Meier 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 summarized by treatment group. If data warrant, the Kaplan-Meier estimate for the median duration of response time and the first and third quartiles will be determined along with 95% CIs using the Brookmeyer-Crowley method. The interpretation of results for DOR is limited as DOR is only defined for subjects with a tumor response CR, CRu or PR.

A by-subject listing will be provided for central review and investigator assessed DOR by treatment group.

4.10.3.7 Analysis of Repeat-Bone Marrow Biopsy Data

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.

A summary of the number of subjects with repeat-bone marrow results including overall cellularity, tumor cell infiltration at screening and ongoing maintenance treatment period will be summarized by treatment group.

A by-subject listing of bone marrow biopsies will be generated using the including date and time of bone marrow biopsy performed, overall cellularity, tumor cell infiltration: lymphoplasmacytic cell involvement in the marrow, intertrabecular space (0%-100%), general marrow involvement by lymphoma (0%-100%).

4.10.4 Analyses of Exploratory Efficacy Endpoints / Variables

BOR up to Week 28 based on central radiology review based on the Lugano criteria (Cheson 2014[14]) will be summarized using frequency and percentage with corresponding 95% CI by treatment group for subjects with PET data in the ITT Analysis Set. A summary of any discrepancies between response designation via the 1999 IWG criteria (primary endpoint) and Lugano criteria will be provided.

A by-subject listing of the Lugano criteria data will be provided with tumor response assessment at Week 28.

4.11 Safety Analyses

All safety analyses will be based on the SAF.

4.11.1 Analysis of Extent of Exposure

Exposure summary will be based on the actual dose administered [mg] collecting in the eCRF.

$$\text{Duration of exposure [weeks]} = \frac{\text{last administration date} - \text{first administratin date} + 1}{7}$$

Descriptive summaries will be provided for

- duration of exposure by treatment group
- cumulative actual dose by treatment period (induction, maintenance, overall) and treatment group
- cumulative planned dose by treatment period (induction, maintenance, overall) and treatment group
- dose interruptions, missed doses, dose delays and discontinuations by treatment period (induction, maintenance, overall) and treatment group.

A by-subject listing of study drug exposure will be provided, including infusion start date/time, end date/time, medication kit ID, actual administration dose, dose delay, dose reduction, dose interruption, dose not done, reason of not done and infusion-related reaction.

4.11.2 Analysis of Adverse Events

All reported terms for AEs will be coded using the latest version of MedDRA version 21.1 or the latest. Before database lock the latest version of MedDRA will be used to code the AE terms for all study subjects. The US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI-CTCAE version 5.0) will be used by investigator to assess the severity grade of all AEs.

For all AE tables, subjects will be counted once for each MedDRA PT and each SOC. Unless specified otherwise, AEs will be summarized in the alphabetical order of SOC and then decreasing frequency of PT within the SOC for the treatment group. If the frequency of PT within the SOC is tied, PT will be sorted alphabetically. Summaries by PT will be sorted by decreasing frequency according to the "DRL_RI" subject incidence.

TEAEs are defined as any AE occurring or worsening on or after the first dose of study treatment. AEs which are already present before the first study treatment and increase in severity after the first study treatment will be considered as TEAEs. Pre-existing AEs before the first study treatment with no increase in severity after the first study treatment will not be considered as TEAEs.

All treatment-emergent adverse events (TEAEs) will be summarized by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events.

An overview of AEs by treatment group will be provided, including number of subjects experiencing TEAEs, drug related TEAEs, serious TEAEs,drug related serious TEAEs, TEAEs leading to discontinuation of study medication, drug related TEAE leading to discontinuation of study medication, TEAEs leading to death,. The summary will also be provided for subgroups age group (< 60, ≥ 60 years), gender and race.

Imputation of partial dates of AE record is described in Appendix 2 Partial Date Conventions.

A by-subject listing of all AEs will be provided by treatment group and will include AE term (SOC, PT, and Verbatim term), start date/time and corresponding study day, end date/time and corresponding study day, severity, infusion related reaction (yes/no), relationship, action taken, outcome, seriousness including criteria of serious adverse event (SAE).

4.11.2.1 Analysis of Pre-Treatment AEs

A pre-treatment AE is defined as any AE with an onset date before the date of first administration of study treatment.

A summary of the number of subjects with pre-treatment AEs by SOC, PT a including the number and percentage of subjects experiencing events will be provided.

4.11.2.2 Analysis of Treatment-Emergent Adverse Events

A summary of the number of subjects with drug related TEAEs by SOC, PT including the number and percentage of subjects experiencing events, separately. TEAEs with incidence by PT ≥5% in either of DRL_RI or MabThera treatment group will be additionally summarized by SOC, PT and CTCAE grade by treatment group.

A summary of TEAEs observed, based on the onset date, during the rituximab induction and maintenance will be summarized separately by treatment groups.

4.11.2.3 Analysis of TEAEs by Severity

A summary of the number and percentages of subjects with TEAEs, number of events will be provided by SOC, PT and by CTCAE grade including the number and percentage of subjects experiencing events. If same event occurred more than once in the same subject, the highest severity grade will be used for the analysis.

4.11.2.4 Analysis of TEAEs by Relationship

A summary of the number and percentages of subjects with TEAEs, number of events will be provided by SOC, PT and by relationship (not related, related, not applicable) including the number and percentage of subjects experiencing events.

4.11.2.5 Analysis of TEAEs by Outcome

A summary of the number of subjects with TEAE outcome into "Not recovered/Not resolved", "Recovered/Resolved", "Recovered/Resolved with sequelae/resolved with sequelae", "Recovering/Resolving", "Fatal", and "Unknown" categories for number of events by treatment group will be provided.

4.11.2.6 Analysis of TEAEs Leading to Discontinuation of Study Medication

A summary of the number of subjects with TEAEs leading to discontinuation of study medication by SOC, PT including the number and percentage of subjects experiencing events will be summarized by treatment group.

A by-subject listing of TEAEs leading to discontinuation of study medication will be provided.

4.11.2.7 Analysis of TEAEs Leading to Death

A summary of AEs leading to death will be summarized by SOC, PT including the number and percentage of subjects experiencing events by treatment group.

A separate summary of related AEs leading to death will be provided by SOC and PT including the number and percentages of subjects by treatment group.

A by-subject listing of TEAEs leading to death will be provided including date of death, primary cause of death and its AE preferred term.

4.11.2.8 Analysis of TEAEs by Overall Anti-Drug Antibodyresult

A summary of TEAEs based on categories of overall Anti-Drug Antibody(ADA) result at EOS/ET (positive or negative) will be provided by SOC, PT, including the number and percentage of subjects experiencing events by treatment group. Overall, ADA result is defined as (binding antibodies (BAb)) result status (positive or negative) at EOS/ET visit.

4.11.2.9 Analysis of Non-Serious AEs

A summary of the number of subjects with non-serious AEs which defined as all AE excluding SAEs. Other AEs with incidence by PT ≥5% will be additionally summarized by SOC, PT and treatment group.

4.11.2.10 Analysis of Infusion-Related Reactions

In the AE eCRF page, an option is provided whether AE is infusion-related or not. Based on that we will have a pre-defined list of IRRs using selected PTs from MedDRA.

Separate summaries of the number of subjects with infusion-related reactions and non-infusion related reactions AEs will be provided by SOC and PT including the number and percentage of subjects experiencing events.

Subgroup analysis will also be performed for infusion-related and non-infusion related reactions by CCI index by SOC and PT including the number and percentage of subjects experiencing events.

Subgroup analysis will also be performed for infusion-related and non-infusion related reactions by tumor grades CCI index by SOC and PT including the number and percentage of subjects experiencing events.

Subgroup analysis will also be performed for infusion-related and non-infusion related reactions by geographical region by SOC and PT including the number and percentage of subjects experiencing events.

A by-subject listing of infusion-related reactions will be provided, including both AEs and non-AEs.

4.11.3 Analysis of Deaths, Serious Adverse Events, and Other Significant Adverse Events

4.11.3.1 Analysis of Serious Adverse Events

Serious TEAEs will be summarized by SOC, PT including the number and percentage of subjects, number of events experiencing events by treatment group.

A summary of related serious TEAEs will be provided by SOC, PT including number and percentages of subjects experiencing events, number of events by treatment group.

A summary of the number of subjects with serious TEAE outcome into "Not recovered/ Not resolved", "Recovered/ Resolved", "Recovered/Resolved with sequelae/ resolved with sequelae", "Recovering/ Resolving", "Fatal", and "Unknown" categories for number of events by treatment group and overall will be provided.

A by-subject listing of SAEs will be provided.

4.11.3.2 Analysis of Deaths

Death and primary cause of death will be summarized by the number and percentage of subjects experiencing events by treatment group.

A by-subject listing of deaths will be provided.

4.11.3.3 Analysis of Events of Special Interest

COVID-19 events in the study are to be considered as Events of Special Interest (EOSIs).

Following summaries will be provided for EOSIs:

- Treatment emergent EOSI will be summarized by SOC, PT including the number and percentage of subjects, number of events experiencing events by treatment group. The same summary will be repeated for non-treatment emergent EOSI.
- Number and percentages of subjects with EOSIs, number of events will be provided by SOC, PT and by severity (mild, moderate, severe, life threatening, leading to death) including number and percentage of subjects experiencing events by treatment group. This summary will be repeated for Treatment emergent and Non-Treatment emergent EOSIs.
- Number of subjects with EOSIs leading to discontinuation of study medication by SOC, PT including number and percentage of subjects experiencing events by treatment group. This will be repeated for repeated for Treatment emergent and Non-Treatment emergent EOSIs.
- EOSIs leading to death by SOC, PT including number and percentage of subjects experiencing events by treatment group. This will be repeated for Treatment emergent and Non-Treatment emergent EOSIs.
- SAEs of special interest by SOC, PT including number and percentage of subjects, number of events experiencing events by treatment group.

4.11.4 Analysis of Clinical Safety Laboratory Data

Clinical safety laboratory data includes hematology, biochemistry, coagulation, and urinalysis and other screening tests. For details of clinical safety laboratory tests, refer to study protocol section 8.3.4.

Clinical safety laboratory data will be summarized for each test by visit and according to maximum NCI-CTCAE grade by treatment group. Change from baseline will also be summarized by visit and treatment group.

The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. For a laboratory test for which an NCI CTCAE scale does not exist the shift table will be summarized using the categories

- L for values below the lower limit of the reference range
- N for values within the reference range
- H for values above the upper limit of the reference range.

A by-subject listing will be provided for laboratory parameters with absolute values by treatment group and overall, with indicator of CTCAE grade if applicable. Subjects with any out of reference range value during the study will be flagged on the listing using the following codes L, N, H as defined above.

The list of laboratory assessments to be included in the outputs is referred to

Appendix 3 Laboratory Assessments. Lab values will be converted to standard unit, as reference in the NCI-CTCAE. For white blood cell (WBC) differentials when only percentages and total leukocyte count are available the absolute values are calculated by multiplying the total number of WBCs by the percentage of each type of WBC and dividing by 100.

4.11.5 Analysis of Vital Signs

Vital signs will include heart rate, blood pressure, respiratory rate, and oral or tympanic body temperature. The results of each scheduled assessment of vital signs, actual and change from baseline values will be summarized at all post-baseline visits by treatment group.

Shift Tables for the transition from baseline among the different categories in the low/normal/high categories will be provided by treatment group, see Appendix 4 Reference Ranges for Vital Signs for definition of categories low/normal/high.

A by-subject listing of vital signs will be provided.

4.11.6 Analysis of Physical Examinations

Body weight, and body system will be summarized by treatment group for scheduled time points using descriptive statistics.

Physical examination findings will be summarized by treatment for scheduled time points using frequency tables.

A by-subject listing of physical examinations will be provided.

4.11.7 Analysis of 12-Lead Electrocardiogram

A summary of actual and change from baseline values of 12-lead electrocardiogram (ECG) data at scheduled visits will be provided by treatment group.

A summary of subjects with designated changes in VR and QT, QTcF, PR, QRS and RR will be provided by treatment group.

A by-subject listing of 12-lead ECG data and findings will be provided.

4.11.8 Analysis of ECOG Performance Status

A summary of ECOG performance status at scheduled visits will be provided by treatment group. The ECOG shift from baseline to highest score during the on-treatment period will also be summarized with categories 0, 1, 2 etc.

A by-subject listing of ECOG performance status will be provided.

4.11.9 Analysis of Immunogenicity Data

Immunogenicity data, i.e., ADA (binding antibodies (BAb)) and neutralizing antibodies (NAb) will be summarized and analyzed descriptively for each scheduled time point (baseline, Week 4, Week 8, , Week 28, Week 44 and Week 52/EOS or ET):

- Number and percentage of subjects with ADA (binding antibodies (BAb)) results (positive or negative) by treatment group and visit; for positive subjects, titer values will be summarized.
- Number and percentage of subjects with NAb results (positive or negative) will be presented by treatment group and visit.

A by-subject listing of immunogenicity data will be provided.

4.11.10 Data Monitoring Committee

The study has a Data Monitoring Committee (DMC) to review periodically study progress and to review the blinded sample size re-estimation (BSSR, see Section 4.13.2) results as per the DMC Charter. The periodic reviews by the DMC include:

- screening, recruitment status, subject disposition
- safety status update of study
    1. TEAEs: severity, relationship, leading to discontinuation of study treatment
    2. SAEs and deaths
    3. Infusion-related reactions

Further details can be found in the DMC Charter.

4.12 Other Analyses

4.12.1 Analysis of Pharmacokinetic Endpoints / Variables

Plasma concentrations of rituximab will be listed and summarized for the PKS by treatment group and visit at which samples were taken. Descriptive statistics will include n, mean, median, min,max ,SD, CV%, geometric mean and geometric coefficient of variation.

Serum values below the lower limit of quantification (LLOQ) will be set to LLOQ/2.

A separate analysis plan for the Population PK modelling will be developed and results will be provided in a separate Population PK Report.

4.12.2 Analysis of Pharmacodynamic Endpoints / Variables

Pharmacodynamic endpoints / variables (see Section 3.2.3 for definitions) will be summarized by treatment group for the PDS.

Peripheral blood B-cell counts by time point will be summarized by treatment group:

- Descriptive statistics (including 95% CIs for means) for Emax.
- AUEC will be calculated using the linear trapezoidal rule. AUEC will be natural log transformed to obtain a point estimate as well as 90% and 95% CIs for the difference of arithmetic means using an ANOVA with study treatment and strata used in the stratified randomization as fixed effects. Point estimate and CIs will be re-transformed to the original scale to obtain point estimate and CIs for the ratio of geometric means.
- Time to B-cell depletion will be descriptively compared by Kaplan Meier curves and 95% CI for the median time to depletion in each treatment group. Subjects without a B-cell depletion will be censored at the date of their last B-cell count up to Week 28 for the Week 28 CSR, up to Week 52 for the Week 52 CSR, respectively.
- Time to B-cell repletion will be descriptively compared by Kaplan Meier curves and 95% CI for the median time to repletion in each treatment arm. Subjects without a B-cell repletion after a B-cell depletion will be censored at the date of their last B-cell count up to Week 28 for the Week 28 CSR, up to Week 52 for the Week 52 CSR, respectively.

A by-subject listing of pharmacodynamic data and endpoints will be provided.

4.12.3 Analysis of Data Related to the COVID -19 Pandemic

A summary of the number and percentage of subjects with visit impact and category due to COVID-19 pandemic will be presented by treatment group. Percentages will be based on ITT Analysis Set. A by-subject listing of visit impact and category due to COVID-19 pandemic will be provided.

COVID-19 laboratory test results will be summarized by visit and treatment group based on the ITT Analysis Set. A by-subject listing for COVID-19 laboratory test results as well as COVID-19 questionnaire will be provided.

4.13 Determination of Sample Size

4.13.1 Determination of Initial Sample Size

Published data for rituximab treatment versus a "watch and wait" strategy in the first line treatment of LTBFL (Ardeshna 2014[Error! Reference source not found.]) revealed a treatment effect [redacted]

CCI [redacted]

CCI [redacted]

4.13.2 Blinded Sample Size Re-Estimation

Due to the uncertainties regarding the assumed BORRs, a BSSR was planned and performed when BOR up to Week 28 was available for the first 50% of initially planned subjects. The sample size was re-estimated on the basis of the observed pooled BORR to maintain statistical power of at least 80%. The same assumptions used in the initial sample size calculation were used except for the initially assumed BORRs. A reduction of sample size below the initial number of 250 subjects was not allowed. Full BSSR details are available in a separate BSSR SAP, especially a detailed BSSR algorithm and extensive simulations demonstrating maintenance of the type-I-error probability.

Based on the observed pooled BORR up to Week 28 and the same assumed difference as in the initial assumptions (Section 4.13.1), the revised total sample size obtained in the BSSR was 312 subjects (156 per group) to be randomized.

4.14 Changes in the Conduct of the Study or Planned Analysis

In the protocol page 82, section 9.4.5 says that AUEC will be investigated using a linear mixed-effects model with treatment as a fixed effect and subject as a random effect.

However, as this is a parallel group study, AUEC will be analyzed using ANOVA with treatment as fixed effect.

The intercurrent events in statistical analysis plan are more specific and statistical methods for handling of intercurrent events are explained in detail.

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Appendix 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							
FLIPI2 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
CT Scan[13] or [18F]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; Ctrough = trough plasma concentration; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS/ET = End of Study/Early Termination;[18F]FDG-PET: fluorine-18-fluorodeoxyglucose positron emission tomography; FL = follicular lymphoma; [redacted]; 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) until 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 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 6 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, blood pressure, pulse rate, and respiratory rate will be recorded at each time point. Vital signs will be monitored every 30 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 a urine pregnancy test on Day 1 prior to randomisation, and all subsequent study drug dosing visits. 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 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. 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 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.

[16] All the baseline assessments must be reviewed by the investigators for final eligibility assessment before randomisation of the subject

[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 weekly i.v infusions 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.

Appendix 2 Partial Date Conventions

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, and partial dates with both missing day and month will be assumed to be June 30. Otherwise, the following rules in Table 12 and Table 13 will be applied.

Table 12 Algorithm for Prior/Concomitant Medications

Start date	Stop date	Action
Known	Known	If stop date is prior to date of randomization, considered as prior only; if start date is prior to date of randomization, and stop date is on or after date of randomization, considered as both prior and concomitant; if start date is on or after date of randomization, considered as concomitant only.
	Partial	Last day of the month and December will be used if day/month of stop date is missing. If imputed stop date is prior to date of randomization, considered as prior only; if start date is prior to date of randomization, and imputed stop date is on or after date of randomization, considered as both prior and concomitant; if start date is on or after date of randomization, considered as concomitant only.
	Missing	If start date is prior to date of randomization, considered as both prior and concomitant; if start date is on or after date of randomization, considered as concomitant only.
Partial	Known	First day of the month and January will be used if start day/month is missing. If stop date is prior to date of randomization, considered as prior only; if imputed start date is prior to date of randomization, and stop date is on or after date of randomization, considered as both prior and concomitant; if imputed start date is on or after date of randomization, considered as concomitant only.

Start date	Stop date	Action
	Partial	First day of the month and January will be used if start day/month is missing. Last day of the month and December will be used if day/month of stop date is missing. If imputed stop date is prior to date of randomization, considered as prior only; if imputed start date is prior to date of randomization, and imputed stop date is on or after date of randomization, considered as both prior and concomitant; if the imputed start date is on or after date of randomization, considered as concomitant only.
	Missing	First day of the month and January will be used if start day/month is missing. If imputed start date is prior to date of randomization, considered as both prior and concomitant; if imputed start date is on or after date of randomization, considered as concomitant only.
Missing	Known	If stop date is prior to date of randomization, considered as prior; if stop date is on or after date of randomization, considered as both prior and concomitant;
	Partial	Last day of the month and December will be used if day/month of stop date is missing. If imputed stop date is prior to the date of randomization, considered as prior; if imputed stop date is on or after date of randomization, considered as both prior and concomitant.
	Missing	Considered as both prior and concomitant.

Note: If recorded start date or imputed start date of the medication is after date of last dose of study treatment, it will neither be classified as prior or concomitant medications, just set the category to missing.

Table 13 Algorithm for Treatment-Emergent Adverse Events

Start / increase severity date	Stop date	Action
Known	Known	TEAE if start date on or after date of first dose of study treatment.
	Partial	TEAE if start date on or after date of first dose of study treatment. Last day of the month and December will be used if stop day/month is missing.
	Missing	TEAE if start date on or after date of the first dose of study treatment.
Partial, but known components show that it cannot be on or after first study drug taken date	Known	Not a TEAE. First day of the month and January will be used if start day/month is missing.
	Partial	Not a TEAE. First day of the month and January will be used if start day/month is missing. Last day of the month and December will be used if stop day/month is missing.
	Missing	Not a TEAE. First day of the month and January will be used if start day/month is missing.
Partial, could be on or after first study drug taken date	Known	TEAE, if stop date is after first dose of study treatment. Date of first dose of study treatment will be used if start date is in same month/year as date of first dose of study treatment, or first day of the month and January will be used if the start day/month is after date of first dose of study treatment. Not TEAE, if stop date is prior to date of first dose of study treatment. First day of the month and January will be used if start day/month is missing.
	Partial	TEAE. Date of first dose of study treatment will be used if start date is in same month/year as date of first dose of study treatment, or first day of the month and January will be used if start day/month is after date of first dose of study treatment. Last day of the month and December will be used if stop day/month is missing.
	Missing	TEAE. Date of first dose of study treatment will be used if start date is in same month/year as date of first dose of study treatment, or first day of the month and January will be used if start day/month is after date of first dose of study treatment.

Start / increase severity date	Stop date	Action
Missing	Known	TEAE if stop date is on or after date of the first dose of study treatment.
	Partial	Last day of the month and December will be used if the stop day/month is missing. If imputed stop date is on or after the date of first dose of study treatment, then a TEAE; if the year is missing, considered as a TEAE.
	Missing	TEAE

Appendix 3 Laboratory Assessments

- Laboratory tests detailed in Table 14 will be performed by local laboratories.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 14 Protocol-Required Safety Laboratory Assessments

Laboratory assessment	Parameter	
Hematology	Hematocrit Platelet count Red blood cell count Total hemoglobin	White blood cell with differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)[1]
Coagulation	Prothrombin time	
Clinical Chemistry	β-2 microglobulin Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Creatinine Creatinine clearance (Cockroft-Gault formula)	Gamma-glutamyl transpeptidase Lactate dehydrogenase Phosphate Potassium Random serum glucose Sodium Total bilirubin Total protein Uric acid

Laboratory assessment	Parameter	
Routine urinalysis (by dipstick)	Specific gravity	Bilirubin
	pH	Urobilinogen
	Protein	Nitrite
	Glucose	Leukocyte esterase
	Blood	Microscopic examination[2]
	Ketones	
Other Screening Tests	Follicle stimulating hormone (as needed in women of non-childbearing potential only: women with cessation of menstruation for ≤ 2 years, peri-menopausal women with inconclusive menopausal evidence 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 testing3: 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.

Appendix 4 Reference Ranges for Vital Signs

Table 15 Reference Ranges for Vital Signs

Vital sign	Criteria
Systolic blood pressure	For baseline value High > 160 mmHg, for post-baseline value High > 160 mmHg
	For baseline value Low < 90 mmHg, for post-baseline value Low < 90 mmHg
Diastolic blood pressure	For baseline value High >100 mmHg, for post-baseline value High > 100 mmHg
	For baseline value Low < 60 mmHg, for post-baseline value Low < 60 mmHg
Pulse rate	For baseline value High > 100 bpm, for post-baseline value High > 100 bpm
	For baseline value Low < 60 bpm, for post-baseline value Low < 60 bpm
Respiratory rate	For baseline value High > 25 pm, for post-baseline value High > 25pm
	For baseline value Low < 12 pm, for post-baseline value Low < 12 pm
Temperature	For baseline value High > 38 C, for post-baseline value High > 38 C
	For baseline value Low < 35 C, for post-baseline value Low < 35 C

Appendix 5 Visit Windowing Rule for Tumor Assessments

Table 16 Visit Windowing Rule for Tumor Assessment

Visit	Start day	Target Day	End Day
Baseline	1	1	1
Week 12	56	84	112
Week 28	168	196	224
Week 52/EOS	336	364	392

Note: Subject who prematurely terminated from the study will be mapped to correct visit based on target day.

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