25 July 2024
EMA/565284/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ituxredi

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/006224/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BLQ	Below the limit of quantification
BSA	Body surface area
BPD	Biological Product Development
BORR	Best overall response rate
CDC	Complement-dependent cytotoxicity
CHMP	Committee of Human Medicinal Products
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRP	C-reactive protein
CRu	Unconfirmed complete response
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CQA	Critical quality attributes
DMARD	Disease-modifying antirheumatic drugs
FP	Finished product
DRL	Reddy Holding GmbH, an entity of Dr. Reddy's Laboratories in the European Union (EU)
DRL_RI	Dr Reddy's rituximab
AS	Active substance
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EOSI	Events of special interest
EU	European Union
GCP	Good Clinical Practice
GPA	Granulomatosis with polyangiitis
HAQ-DI	The Health Assessment Questionnaire Disability Index
IRR	Infusion-related reactions
ITT	Intent-to-Treat
IV	Intravenous
LTB-FL	Low tumour burden follicular lymphoma
LLN	Lower limit of normal
MCB	Master cell bank

MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of action
MPA	Microscopic polyangiitis
MTX	Methotrexate
Nab	Neutralising antibodies
NHL	Non-Hodgkin's lymphoma
ORR	Overall response rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PP	Per protocol
PR	Partial response
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred term
RA	Rheumatoid arthritis
RP	Reference Product
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TMRC	Time-matched rituximab concentrations
TNF	Tumour necrosis factor
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Reddy Holding GmbH submitted on 25 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Ituxredi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Non-Hodgkin's lymphoma (NHL)

Ituxredi is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Ituxredi maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy.

Ituxredi monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Ituxredi is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Ituxredi in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

Chronic lymphocytic leukaemia (CLL)

Ituxredi in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Ituxredi or patients refractory to previous Ituxredi plus chemotherapy.

Rheumatoid arthritis

Ituxredi in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Ituxredi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and microscopic polyangiitis

Ituxredi, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Ituxredi, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

Pemphigus vulgaris

Ituxredi is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is: MabThera

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form:
  MabThera (rituximab) 100mg, 500 mg Concentrate for solution for iv infusion
  1400 mg, 1600 mg solution for sc injection
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 02-06-1998
- Marketing authorisation granted by:
  - European Union
- Marketing authorisation number: EU/1/98/067/001-004

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
17 March 2011	EMEA/H/SA/2054/1/2011/III	Jan Mueller-Berghaus, Thomas Lang
09 November 2017	EMEA/H/SA/2054/2/2017/II	Ole Weis Bjerrum, Christian Gartner
25 April 2024	EMA/SA/0000167470	Larissa Higgins, Vilma Petrikaite

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Proposed physicochemical, functional and stability tests and acceptance criteria for the drug product; control strategy, validation of virus reduction for manufacture of the drug product; assessment of active substance manufacturing and process performance qualification for post-approval change; analytical comparability, biosafety, and leachable and extractable assessments as part of process performance qualification; acceptability of drug product manufactured with the commercial process for use in PK/PD studies
- Need for non-clinical animal studies
- Design of the planned PK/PD study regarding patient population, primary and secondary endpoints and selected equivalence margins; PK data requirements to initiate phase 3 clinical development; adequacy of the proposed Phase III study design, including the study population, choice of comparator, primary endpoint, equivalence margin, estimation of treatment effect, sample size and methods for handling data; acceptability of proposals regarding ethnicity of the patient population, extrapolation to indications other than NHL; adequacy of the safety database; scope of data to be collected during post-marketing surveillance; adequacy of the clinical package to support biosimilarity and marketing authorisation

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	25 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	15 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 December 2023
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
- A GMP inspection at manufacturing site of drug substance and drug product (including quality control testing and packaging activities) between 20 and 29 May 2024. The GMP certificate for the site as a result of the inspection was issued on 26 June 2024	17/07/2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 February 2024
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ituxredi on	25 July 2024

2. Scientific discussion

2.1. Problem statement

Ituxredi (rituximab) is a proposed biosimilar to reference medicinal product MabThera. The intended indications are the same as those currently approved for MabThera:

Non-Hodgkin's lymphoma (NHL)

Ituxredi is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy.

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Ituxredi monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Ituxredi is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Ituxredi in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

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See section 5.1 for further information.

Rheumatoid arthritis

Ituxredi in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Ituxredi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

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Ituxredi, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Ituxredi, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

Pemphigus vulgaris

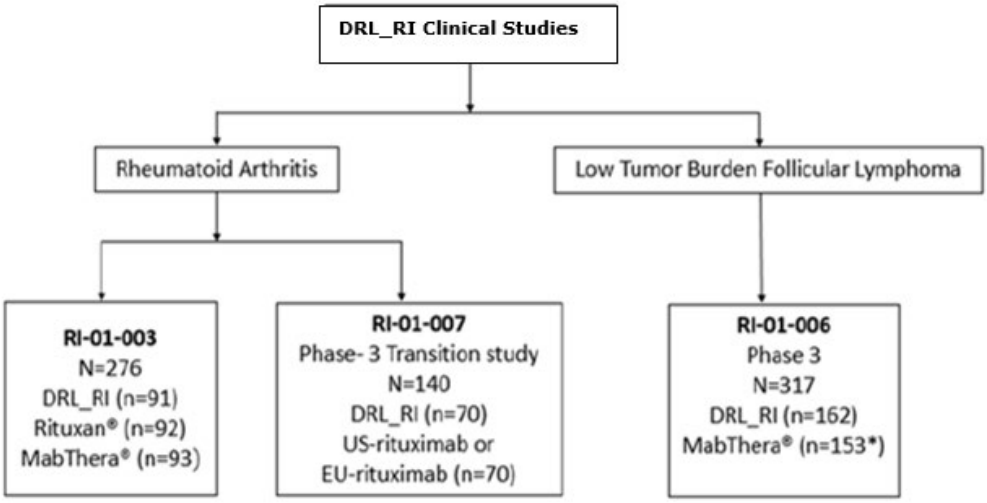
Ituxredi is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

2.2. About the product

Rituximab binds specifically to the transmembrane antigen CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis. The clinical program for the rituximab biosimilar Ituxredi consists of three studies:

Figure 1 Overview of the clinical program for the rituximab biosimilar Ituxredi



Abbreviations: DRL_RI = Dr. Reddy's rituximab; EU-rituximab = European Union approved rituximab (MabThera); N = number of all patients randomised; n = number of patients in Safety Analysis Set included under each treatment group; US-rituximab = United States licensed rituximab (Rituxan).

* Two subjects in the MabThera group were randomised but not dosed hence, data was missing.

Study RI-01-003 is a randomised, multicentre, double-blind, parallel 3-way PK equivalence study comparing Ituxredi to Rituxan and MabThera in combination with non-biological disease-modifying antirheumatic drugs (DMARDs) in 276 patients with active RA. The study has been completed.

Study RI-01-006 is a randomised, double-blind, parallel group, Phase 3 study to compare the efficacy, safety, PK, PD, and immunogenicity of DRL_RI with MabThera in 317 patients with previously untreated, stage II-IV, CD20-positive LTB-FL.

All study data up to and including the Week 28 study visit have been included for study RI-01-006 in the initial submission. With regard to subject disposition, all available data up to the cut-off date of 21 September 2022 were included (first subject was screened on 15 May 2019, and the last subject completed the Week 28 visit on 13 September 2022).

The final and complete CSR for study RI-01-006 including the full data set was submitted.

Study RI-01-007 is a randomised, double-blind, parallel group, multicentre single transition Phase 3 study in 140 RA patients who had already completed at least 1 full course of treatment with Rituxan or MabThera to assess the immunogenicity and safety after they were subsequently switched to DRL_RI compared to patients who continued treatment with the respective Rituxan or MabThera. This study was conducted in accordance with US-FDA requirements and is completed.

2.3. Type of application and aspects on development

The legal basis for this application refers to: Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.

2.4. Quality aspects

2.4.1. Introduction

Rituximab, the active substance contained in Ituxredi, also referred as DRL_RI, is a recombinant chimeric mouse/human monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology.

Ituxredi was developed as biosimilar to the reference medicinal product (RMP) MabThera.

The finished product is presented as a clear to opalescent, colourless to yellowish concentrate for solution for infusion, containing 100 mg and 500 mg of rituximab as active substance. Other ingredients are: sodium citrate, citric acid, polysorbate 80, sodium chloride and water for injections (WFI).

Ituxredi 100 mg and 500 mg concentrate for solution for infusion is supplied in 10 ml or 50 ml clear type I vials respectively. Each ml contains 10 mg of rituximab.

Ituxredi is supplied in packs of 1 or 2 vials.

2.4.2. Active substance

2.4.2.1. General information

Rituximab (DRL_RI) active substance (AS) is a monoclonal antibody that binds specifically to the CD20 cell surface antigen, a non-glycosylated phosphoprotein, found on pre-B cells, normal B cells and malignant B cell tumors.

The antibody is an IgG1 kappa immunoglobulin with a single site of N-linked glycosylation at Asn301. Fifteen distinct glycan species, corresponding to complex biantennary oligosaccharides, have been detected and identified. In addition, the antibody includes a mixture of charge variants, in part due to variable hydrolysis of the C-terminal lysine on the antibody heavy chains and cyclisation of the N-terminal glutamine on the heavy and light chains to form pyroglutamate.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the FcγRIIIa receptors on the

surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturer

The active substance manufacturing site was not inspected for GMP compliance by any of EEA authority or by an authority of countries where GMP mutual recognition agreements (MRAs) apply. Therefore, an inspection of the site by an EEA authority needed to be performed in order to confirm GMP compliance. Given that a positive outcome of that inspection is a prerequisite for an approval in Europe a Major Objection was raised.

An on-site inspection of the facility was carried out by Regierung von Oberbayern – Sachgebiet 53.2 – Pharmazie, District Government of Upper Bavaria – section area 53.2 Pharmacy, Germany from February 20-24 & February 26-29, 2024. Following that, a virtual inspection was carried out on April 30, 2024. The GMP Inspection Report was received from the inspectorate, and submitted with the responses along with the applicant's proposed CAPA plan. A copy of that certificate confirming compliance with GMP has been provided which resolved this Major Objection.

Description of the active substance manufacturing process

DRL_RI AS is produced from a recombinant CHO cell line. The manufacturing process of DRL_RI AS is composed of cell culture and purification processes.

A working cell bank (WCB) vial is thawed and cells are expanded in a chemically defined growth medium to generate the cell inoculum. A series of spinner flasks and fermenters of increasing volume are used to expand the cell mass to generate sufficient cells for inoculation of the stirred-tank production fermenter. At the end of the seed fermenter stages, the seed culture is aseptically transferred to a production fermenter. The cell density is measured by offline sampling of the bioreactor. The clarified harvest is then purified using a series of chromatography and filtration steps. Lastly, it is processed through sterile filter to yield DRL_RI AS and subsequently frozen for storage.

Control of materials

Reagents, solvents and auxiliary materials used in the manufacture of DRL_RI are listed. For compendial materials reference is made to the respective monographs (Eur. Ph., United States Pharmacopeia/National Formulary monograph (USP NF)), which is acceptable for the materials listed.

Specifications and acceptance criteria for non-compendial materials are provided. All the resins, membranes and filters used in the manufacturing process are tested and released as per quality standards before its use in the manufacturing process.

The genes for expression of the rituximab light and heavy chains were reverse engineered and cloned into plasmids. The plasmids were transferred to a contract research laboratory where they were used to generate replication incompetent retroviral vectors. The retroviral vectors were subsequently used to introduce the heavy and light chain gene sequences.

The starting materials and procedures for generation of the retroviral vectors are described in the dossier. LC and HC gene sequence in retroviral vector plasmid is presented in the dossier. Description of the development of retroviral vector packaging cell Line is sufficiently described. Results of characterization tests performed on MCB are provided. Certificates of analysis for all animal-derived materials (FBS and trypsin) used in the propagation of the research cell bank, MCB and working stock are provided. Origin and description of CHO-S host cell line raises no concerns. Results of characterization tests performed on CHO-S MCB are included. The clonal cell line was expanded

through several serial passages in suspension cell culture and cryopreserved. The cell line was re-assigned to be Passage 0 when it was isolated from the clonal selection plate. The cryopreserved cells were tested for freedom from bacteria, fungi, mycoplasma and replication competent retrovirus before manufacture of a MCB.

A two-tiered cell banking system was established. The MCB was manufactured by expansion from one vial of the clonal cell line. The MCB was extensively tested for identity, morphology, and freedom from adventitious agents, including mycoplasma, bacteria, fungi and animal or human viruses. The established cell banks (MCB and WCB) are stored in the Cryovial storage vessels with automated filling system, located in access restricted areas. The cell bank storage units are monitored regularly. The long-term stability of the cell banks is monitored continuously as per ICH Q5D guidelines.

The genetic stability of the production cell line was evaluated in the MCB, WCB, end of production cell bank (EPCB), as well extended-passage cell banks indicating genetic stability of the MCB . The requirements for establishment and qualification (retesting scheme with acceptance criteria) of future new WCB are provided.

Controls of critical steps and intermediates

Initially, paragraphs on the majority of pages of section 3.2.S.2.4 Controls of Critical Steps and Intermediates, were missing and therefore the overall context could not be completely assessed. The Applicant was asked to carefully review the documents and provide them in a readable manner. The Applicant was asked to revisit the proposed control strategy and provide a revised concept in order to ensure that the process control (input and output parameters) result in active substance of the intended quality. For in-process controls, neither a risk assessment nor a differentiation between critical and non-critical controls is made. It was also unclear what the consequences are in case where NOR or PAR ranges were not met. The revised strategy should be revised (Major Objection).

With the responses and based on the outcome of the process characterization, process parameters were classified as critical process parameter (CPP) and non-critical process parameter (NCPP) with proven acceptable range (PAR) and normal operating range (NOR) being provided for each parameter of identified process stages. In section 3.2.S.2.2 Description of Manufacturing Process and Process Controls, for the different steps in-process controls are defined together with acceptance criteria..

Overall, the approach to identify critical quality attributes (CQA), process parameters (PPs) and critical process parameters (CPPs) is in accordance with principles defined in ICH Q8/Q9. Scale-down models qualification data were provided, and the results obtained from process characterization studies were further provided in graphic format using prediction profiles for the upstream process (USP) and downstream process (DSP). The methods for in-process controls e.g. mycoplasma, adventitious viruses and filter integrity testing are described. Bioburden control strategy is described in detail and justified.

Overall, the revised control strategy was acceptable and adequately justified and the Major Objection was considered resolved.

Active substance manufacturing process validation

Consecutive AS batches were executed as part of process performance qualification (PPQ) and evaluated to demonstrate the robustness of the process. For all batches predefined acceptance criteria for NCPPs and PIPs (process performance indicators) are met. Also, for Seed fermenter (SF) stages the acceptance criteria (AC) were met. Process performance data at production fermenter (PF) stage demonstrate that the pre-defined AC were met.

For the downstream process all predefined acceptance criteria (for process parameters and process indicators) were met, in particular for CPPs and PIPs, indicating that the process is robust and delivers

consistent product quality. Process related impurities, are consistently removed during the manufacturing process. PPQ batches samples were evaluated to test for all process related impurities. Hold time study for DRL_RI process intermediates was carried out. Final filter validation data is presented. Compatibility study results and extractables study results are provided. Data on compatibility and leachable study for filter raises no concerns. Risk assessment was performed for leachables from single-use equipment in accordance to EMA/CHMP/BWP/187338/2014 guidelines. The assessment covers all disposable materials/equipment that are coming into direct contact with the product The conclusion from risk assessment that all the polymeric product contact materials used in manufacturing process have low risk and is considered safe for its intended usage in process is endorsed.

Overall, the active substance manufacturing process is considered validated.

Manufacturing process development

During process developments refinements to the upstream cell culture process were carried out with the following objectives: reduction in the percentage of aggregates, alignment of the glycan profile with the reference medicinal product (RMP), control of the charge variants. Specifically, cell culture process development was primarily targeted at refining the proportion of afucosylated glycan species which are correlated with potency in *in vitro* assays of antibody mediated cell killing. Purification process development was aimed at reducing the level of aggregates and the proportion of basic charge variants in the AS. The final manufacturing process is used for all the studies including non-clinical, clinical and PPQ and is proposed for commercial manufacturing. AS manufacturing process for DRL_RI was scaled up with consequent changes that are related to scale up requirement. The larger scale process follows essentially the same steps as smaller scale process with few adaptions to accommodate the larger scale.

Initially comparability between active substance batches from different manufacturing scales has not been sufficiently demonstrated. Analytical data for batches from subsequent campaigns (release testing, extended characterisation panel including forced degradation) was requested to be presented in section 3.2.S.2.6 Manufacturing Process Development to support the comparability claim. The comparative and conclusive assessment of the attributes belonging to extended characterisation panel (e.g. primary structure, detailed glycan profile) for first reference standard, Phase I and Phase III and PPQ AS batches should be provided and discussed in 3.2.S.2.6. (Major Objection).

With the responses the Applicant provided further comparability data (in-process performance and AS release data) which indicate that the quality of DRL_RI manufactured at higher scale is sufficiently comparable to the product manufactured at initial scale. Based on physicochemical and functional data it can be concluded that materials throughout the development can be considered sufficiently comparable. This is supported by comparative stress stability. The information provided is adequate and sufficient and this Major Objection was considered resolved.

Characterisation

Structure and other molecular characteristics of the DRL_RI AS were assessed based on the physicochemical attributes including primary, secondary and higher order structure, variant characterization and functional attributes including mechanism of action, target binding and Fc binding. The different features will be discussed in more detail further below when assessing biosimilarity as structural and functional characteristics of DRL_RI should be consistent with expectations for a biosimilar rituximab monoclonal antibody.

Product variants are expected for therapeutic protein products due to the inherent complexity and heterogeneity of biological molecules as well as their manufacturing processes. The variants expected for monoclonal antibodies primarily include glycan variants arising from differential glycosylation during the cell culture process, charge variants primarily due to N-, C-terminal and other amino acid modifications like deamidation and oxidation etc., size variants due to fragmentation and clipping of product. Rituximab is a glycosylated molecule with a single N-linked glycosylation site at Asn301 in the Fc region of the antibody heavy chain.

The antibody binds specifically to the CD20 cell surface antigen found on pre-B cells, normal B cells and malignant B cell tumors. In *in vitro* assays, the DRL_RI antibody mediates the lysis of CD20-expressing target cells through complement C1q binding to the antibody Fc domain (complement dependent cytotoxicity), or through binding of the Fc domain to FcγRIIIa expressed on the surface of cytotoxic effector cells (antibody dependent cellular cytotoxicity). DRL_RI is also observed to elicit apoptosis in CD20-expressing target cells *in vitro*. The analysis included functional assays (apoptosis, CDC, ADCC), as well as target antigen (CD20) binding and Fc binding assays (including C1q, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIb, FcγRIIIa and FcRn). The impact of glycan, charge and size variants was also evaluated in selected functional assays to establish the structure-function correlation.

Process related impurities are either efficiently removed by the manufacturing process or do not pose a risk to patient safety based on risk assessments and/or semi-quantitative assessment performed under worst-case scenario and comparing the calculated amounts to permitted daily exposure (PDE). Product-related variants were identified and characterized either they are controlled via release specifications (size and charged variants), or their presence is negligible because of low abundance or "normal" functional activity. The information provided in this section is sufficient.

2.4.2.3. Specification

The active substance release and shelf life specifications include general characteristics, strength, identity, purity and impurities, potency and safety.

Specifications and limits for control of DRL_RI active substance are provided. Method used for extended characterisation are also described. The potency assay was demonstrated to be precise and robust covering the proposed limit set within the specifications.

The glycan specifications for AS and Finished Product (FP) were further revised based on the extensive evaluation of DRL_RI batches The proposed narrowed new limits are acceptable.

For HCP determination the applicant uses an ELISA kit. Validation results indicate that the assay is suitable for HCP determination at different stages of the manufacturing process including the AS stage. The method was validated for specificity, linearity/range, accuracy, precision, limit of quantitation (LoQ) and robustness parameters.

Recovery of bioburden was observed for all the prescribed microorganisms when spiked to all active substances batches and formulated active substance samples far within range indicating suitability of the method.

Overall, the active substance release and shelf life specifications are considered acceptable.

Analytical methods

Detailed descriptions (SOPs) of the analytical procedures are provided.

The analytical methods used for lot release testing and stability testing of DRL_RI DS have been either verified for their intended purpose (compendial methods) or being validated in-house (non-compendial

methods). Tests for physical appearance , pH, endotoxins and bioburden are performed in accordance with European compendial procedures.

Summaries of qualification of analytical procedures for characterisation and for comparing the attributes of DRL_RI to the RMP were provided too.

The information provided is sufficient.

Batch analysis

Several batches of DRL_RI active substance manufactured have been produced and released to date, of which some were produced at a small scale and rest were produced at a larger scale. All batches met the acceptance criteria defined at the time of testing.

Reference Material

An internal reference standard (IRS)) was established using a manufacturing process representative of the clinical batches. This IRS was used for multiple purposes such as the verification of system suitability and as the reference standard in various analytical procedures used for analytical similarity testing, stability testing, release of clinical and PPQ DRL_RI batches. It is stated that in order to ensure bridging of the initial IRS and the primary IRS, all quality attributes are tested relative to IRS and RMP. The primary reference standard is derived from PPQ DS batch. A working/secondary standard is planned to be established for the commercial release of DRL_RI batches. The information provided is sufficient and acceptable.

Container Closure System

The AS is collected and stored in sterile bags. The Applicant declares that container fulfills Ph.Eur. standards. An Extractables study for DRL_RI AS container closure systems employed for storage of the AS has been conducted. The extractables were analyzed by a variety of analytical techniques to determine organic compounds and elemental impurities. The extractable study design and to overall approach for safety concern threshold determination is considered acceptable. Results of the leachable study did not raise concerns.

2.4.2.4. Stability

The stability studies of the batches from PPQ campaign and the results under real and accelerated condition are found to be consistent with the data from prior AS campaign. Although some process parameters were modified or appended in the PPQ campaign based on the process characterisation studies these are not considered major changes in the proposed commercial manufacturing process as compared to clinical process and therefore the batches can be considered representative for the PPQ batches manufactured with the process to be commercialized.

Forced degradation stability of DRL_RI AS batches were evaluated. Based on the data obtained, it was concluded that the forced degradation profiles and the extent of changes were comparable under stress conditions.

The stability study of AS was conducted in its designated container closure systems. The DRL_RI AS stored under real time conditions did not show changes in the physicochemical attributes Data from forced degradation studies indicate good stability of DRL_RI AS since no abnormal trends were observed. Freeze-thaw stability investigation suggest that the DRL_RI AS is stable up to two freeze thaw cycles and can withstand the inherent product quality attributes.

Based on the review of the stability data provided the proposed shelf life for the active substance is acceptable.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is formulated as a sterile, preservative-free, concentrated aqueous solution for infusion composed of 10 mg/mL of the active ingredient - rituximab - in a citrate buffer, sodium chloride and polysorbate 80 and water for injection. The FP is supplied in single use, 10 mL or 50 mL Type 1 glass vials. The vials are closed with grey, fluoropolymer-laminated, butyl isoprene rubber stoppers covered by an aluminium flip-off seal with a polypropylene cap.

All excipients are compendial and conform to the quality standards specified in the Ph. Eur. The finished product does not contain any novel excipients or any excipients of human or animal origin.

The choice of excipients is described in sufficient detail. The Applicant has presented a short summary of formulation development. Compliance of the applied product with guideline EMA/CHMP/QWP/805880/2012 Rev. 2 is also discussed. The physicochemical and biological characteristics of the FP potentially relevant to its stability and clinical performance include pH, osmolality, aggregate content, charge variants and potency.

Initially the manufacturing process development data provided was not sufficiently detailed and very limited information was presented. Only a tabular summary of changes introduced to the manufacturing process as well as comparability studies of batches manufactured in small scale and larger scale have been presented which was not sufficient. It should be described how critical parameters that impact on product performance were identified and need to be controlled to ensure product quality. Results of process development studies should be provided; the impact of control of process parameters during each step should be experimentally evaluated. This was raised as a Major Objection. With the responses sufficiently detailed information on the manufacturing process development has been presented, as further discussed below, and this Major Objection was considered resolved.

The FP is supplied in single use 10 mL or 50 mL USP Type 1 glass vials. The excipients and their approximate concentrations were selected based on the inactive ingredients reported on the reference product label. Early manufacturing process was established based on prior knowledge and experience, and with an aim to achieve the desired target product profile and ensure consistent CQAs. Manufacturing process changes were introduced over the development lifecycle of DRL_RI finished product by refining the manufacturing processes and ensuring consistent process performance. Process changes during Phase-I, Phase-III and PPQ were introduced. Process characterization studies were conducted for unit operations, where risk was medium/high and subsequently derisked by demonstrating that the proposed operating range of parameters consistently produces FP with the desired CQAs. Manufacturing process changes were introduced over the development lifecycle of DRL_RI FP by refining the manufacturing processes and ensuring consistent process performance. The process changes during Phase-I, Phase-III and PPQ and an impact risk assessment has been provided. Results from release testing at FP stage show that product quality attributes are within the specification limits. Small differences can be seen in certain quality attributes such as glycan content and charge variants which do not significantly result in functional differences and or clinically meaningful differences. Thus, it can be considered that the quality of DRL_RI finished product manufactured at larger scale is sufficiently comparable to the product manufactured at small scale. Data indicate that DRL_RI Phase-III and PPQ batches are sufficiently comparable.

DRL_RI FP is filled into either 10 mL or 50 mL (nominal fill volume) clear Type I glass vials. The FP filled vials are closed with 20 mm grey butyl rubber stoppers laminated with a fluoro-polymer coating, conforming to the requirements for rubber closures for aqueous parenteral preparations. Stoppered vials are capped with 20 mm, flip-off seals. The aluminum seal completely covers the rubber stopper and is capped with polypropylene disc. The safety of the container closure system was evaluated based on studies to measure the extractable substances. The container closure system (glass vial) was evaluated for extractable substances. There were no substances extracted from the container closure under extreme conditions that presented a safety concern. Extractable amount of chemical compounds, present in grey butyl rubber stoppers was also evaluated. Analysis for N-nitrosamines showed the presence of 1 target compound in ultrapure water (UPW) extract and no target compounds in the DPV (drug product) vehicle (DPV, placebo)) extract above the respective reporting limits. Leachable study revealed that no target element was above the corresponding ICH Q3D PDE in the finished product. With regard to compatibility with process components the Applicant refers to a product contact parts study in which no incompatibilities were observed.

The DRL_RI finished product is a concentrated solution for injection by slow infusion. The FP is diluted to 1 to 4 mg/mL in sterile, pyrogen-free 0.9% (w/v) sodium chloride solution for injection (saline) or 5% dextrose in water. The compatibility of the FP with these infusion diluents was evaluated. The compatibility of the FP with the infusion bottles or bags used for patient administration was evaluated based on the stability of the FP under the intended conditions of use. The compatibility of the FP with the commercially available infusion bottles or bags were verified through stability of the FP under the intended conditions of use.

2.4.3.2. Manufacture of the product and process controls

Manufacturer(s)

The finished product is manufactured and tested for release and stability.

The finished product manufacturer had not been inspected for GMP compliance by any of EEA authority or by an authority of countries where MRA applied. Therefore, an inspection of the site by an EEA authority needed to be performed in order to confirm GMP compliance. Given that a positive outcome of that inspection is a prerequisite for an approval in Europe a Major Objection was raised.

An on-site inspection was carried out by Regierung von Oberbayern – Sachgebiet 53.2 – Pharmazie, District Government of Upper Bavaria – section area 53.2 Pharmacy, Germany from February 20-24 & February 26-29, 2024. Following that, a virtual inspection was carried out on April 30, 2024. The GMP Inspection Report was received from the inspectorate and submitted with the responses along with the applicant’s proposed CAPA plan. A copy of that certificate confirming compliance with GMP has been provided which resolved this Major Objection.

Description of the manufacturing process

The finished product is manufactured from the active substance bulk by dilution of the thawed AS in formulation buffer to obtain the target final protein concentration of 10 mg/mL.

To initiate the preparation of formulated AS and final filtration, the frozen AS is transferred for thawing

Thawed active substance is filtered and the filtered AS is collected. The volume of the active substance is measured and mixed, and a sample is collected for determining the protein concentration. Based on the available quantity Buffer is added to adjust the antibody concentration. The volume of IFDS (intermediate formulated drug substance) is recorded and sample is withdrawn from the vessel for

determination of protein content Before proceeding to filtration, samples of FDS are collected for testing protein concentration and bioburden and the final volume of the formulated active substance is recorded.

The FP is sterilised by filtration. The sterile FP is filled into sterile, depyrogenated Type-1 glass vials, stoppered using sterile, fluoro-polymer coated butyl rubber stoppers and sealed with aluminum seals with polypropylene flip-off cap. 100% Visual inspection is performed manually after completion of filling and sealing operations and as IPC the percentage of visual rejects is implemented. The classification of rejects and the different acceptance criteria for the 10mL and 50mL vials are justified.

Control of critical steps and intermediates

Based on failure mode effect analysis (FMEA) and subsequent process characterization studies CPPs and non-CPPs are defined and classified and a control strategy was implemented consisting of different controls, e.g. in-process quality control (IPQC) and in-process test (IPT). The Normal Operating Range (NOR)/Acceptance Range are provided. Results of the process characterization studies are provided.

Process validation

Consecutive FP batches were manufactured for both the presentations (100 mg/ 10 mL and 500 mg/ 50 mL). The quality attributes of FP and process intermediates from all batches were tested and compared against predefined acceptance criteria. The results of filling step met the acceptance criteria. The process performance qualification studies demonstrate that the FP batches manufactured with the NOR are consistently meeting the pre-defined ranges and acceptance criteria. Thus, consistency of both DRL_RI 100 mg and 500 mg vial manufacturing process can be considered sufficiently validated.

As part of process performance qualification, cumulative hold time of the FP manufacturing process was established. Relative potency determination of the DRL_RI FP batches manufactured using FDS that was subjected to cumulative hold times had acceptable biological activity.

A brief summary of filter validation studies results was provided stating that all the predefined acceptance criteria in the process of sterile filtration of DRL_RI formulated active substance were met. The study included evaluation of product bubble point, bacterial retention test (BRT), extractables, full filtration device compatibility and adsorption studies.

The information is considered sufficient to conclude that filters are suitable for the process. Aseptic processing was confirmed by three successful consecutive media fill runs for each presentation and further routine media fills. The history of media fill results does not raise concerns with regard to the aseptic filling process as no vial investigated show any growth.

To validate the transportation of DRL_RI FP, a transport validation study is completed to cover predefined route and transport conditions of commercial transport and also to confirm the integrity of cold chain pack during transit. The shipping validation protocol is provided and seems to cover relevant aspects. Product quality of the finished product following shipment were analyzed and compared against control (unshipped) samples. Quality attributes met the lot release specification criteria for both shipped and control finished product samples.

Overall, the manufacturing process of the finished product is considered validated.

Control of Excipients

The finished product is formulated to match the reference medicinal product formulation in a solution containing sodium citrate dihydrate, citric acid monohydrate, sodium chloride and polysorbate 80. The excipients are commonly used and are of compendial grade. Specifications and the majority of test methods are in conformance with Ph. Eur. or NF requirements and are considered acceptable. WFI is

generated on-site at DRL. The specifications for WFI are in line with the current USP and Ph. Eur. Examples of in-house analytical test reports are provided. None of the excipients used in the manufacture of DRL_RI FP are of human or animal origin. No novel excipients have been used.

2.4.3.3. Product specification

The finished product specifications include general characteristics, strength, identity, purity and impurities, potency and safety.

Overall, the finished product specifications are considered adequate to control the final product quality.

A risk analysis in accordance with ICH Q3D guideline was performed to evaluate the potential presence of elemental impurities in DRL_RI, confirming that there is no risk of such impurities (all impurities are below 30% PDE for the finished product).

FP was evaluated for nitrosamine impurities introduced during manufacturing process or from raw materials. Nonetheless, initially very limited information on nitrosamines has been presented and not all possible risk sources have been assessed. No clear justification of nitrosamines chosen for analysis has been given. The Applicant was requested to provide an updated risk assessment concerning the presence of nitrosamine impurities in Ituxredi (Major Objection).

A detailed risk assessment considering the CHMP assessment report (EMA/369136/2020) and the current version of "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" was further provided (Nitrosamine Risk Assessment report). A detailed risk assessment of upstream/downstream/FP process and raw materials was performed and confirms that there is no risk of nitrosamine impurities present in DRL_RI finished product.

The updated presented risk assessment is sufficiently detailed. The final conclusion that no nitrosamines risk is identified is accepted and the Major Objection was resolved.

The CCS (glass vial) was evaluated for extractable substances . The extracts were analyzed. There were no substances extracted from the container closure under extreme conditions that presented a safety concern. Extractable Amount of Chemical Compounds, present in grey butyl rubber stoppers was also evaluated.

Analytical methods

Detailed standard operating procedures (SOPs) for the analytical methods are provided. Methods used for testing of the active substance and finished product are the same and discussed above in the respective active substance section.

Compendial methods are verified for the intended use. Method validation of methods used for AS and FP are discussed. Validation of DRL_RI-DP specific methods is adequate and sufficient.

Batch analysis

The results of batch release testing on all DRL_RI finished product batches manufactured were provided. DRL_RI FP batches manufactured from AS at small scale included the investigational batches for the non-clinical studies as well as Phase I clinical trial. The process after Phase I was subsequently scaled up and was used for the Phase III clinical trial. Finally, the batches manufactured as a part of PPQ are also provided.

All batches met the acceptance criteria valid at the time point of testing.

Reference Standard(s)

The same reference standards are used for testing of DRL_RI finished product as for active substance (see active substance section).

Container Closure System

DRL_RI 100 mg and 500 mg finished product presentations are filled into 10 mL and 50 mL clear Type 1 glass vials, respectively. The vials are stoppered with 20 mm butyl rubber stoppers laminated with a fluoro-polymer coating. Stoppered vials are capped with 20 mm, flip-off seals with colored polypropylene disc. Specifications for vial and stopper have been provided.

Each batch of primary packaging components is inspected and tested by the Quality Control unit and is released for use upon conformance to specifications. The CCS (glass vial) was evaluated for extractable substances. There were no substances extracted from the container closure under these extreme conditions that presented a safety concern. Extractable amount of chemical compounds, present in grey butyl rubber stoppers was also evaluated.

Suitability of the container closure system for storage has been confirmed. Risk assessment has been conducted on all materials in contact with product. Extractable/leachable studies have been performed. The information provided is sufficient and adequate.

2.4.3.4. Stability of the product

A shelf life of 3 years when stored at 2°C - 8°C is claimed for the finished product for the unopened vial.

The stability program was designed to assess the quality attributes of rituximab (DRL_RI) finished product under long-term and accelerated storage conditions and complied with relevant ICH Q5C and Q1D guidelines. The complete program covered not only long-term use to assign shelf-life but also to support stability of the product under various conditions, including stress stability, photostability and point-of-use stability.

A comparative physiochemical and functional study was conducted between DRL_RI FP batches, manufactured from different scales indicating sufficient comparability The stress stability studies demonstrate comparable degradation profiles between DRL_RI, RP and RMP. Under stress conditions, all products showed comparable level of changes in relevant structural and functional activity attributes, indicating a high level of similarity of DRL_RI to RP and RMP.

The photostability studies also revealed that exposure of DRL_RI to light has an impact on the quality of FP, concluding that this product is photo labile. However, these studies also revealed that the marketing container provides adequate protection to light to DRL_RI FP.

Overall, the stability data set and the results provided support the proposed shelf life for the finished product of 36 months when stored at the recommended storage condition 2°C - 8°C, protected from light.

For the diluted medicinal product, after aseptic dilution in 0.9% sodium chloride solution, the prepared infusion solution is physically and chemically stable for 60 days at 5°C±3°C and 30 days at 25°C±2°C. After aseptic dilution in 5% dextrose solution, the prepared infusion solution is physically and chemically stable for 48 hours at 2°C - 8°C and 25ºC±2ºC. The results are reflected in the SmPC. It is further stated that from a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at at 2°C – 8°C. This is acceptable.

2.4.3.5. Post approval change management protocol(s)

N/A

2.4.3.6. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – current rev) has been sufficiently demonstrated. The active substance is produced in a serum-free culture medium. No risk material of bovine origin is added during fermentation of DRL_RI. The MCB which has been established is free from TSE-risk substances.

The documentation provided by the Applicant confirms that the active substance and finished product pose negligible risk for transmission of TSE.

Virus safety

The fermentation process of the monoclonal antibody DRL_RI is in a serum-free medium. This minimises a possible contamination for adventitious viruses. The cells used for production of DRL_RI have been extensively screened for viruses

The purification process of DRL_RI includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. In addition, chromatography step also contribute to virus removal.

The removal capacity of small non-enveloped viruses is mainly based on the filtration and chromatographic methods.. In addition, a screening for viruses is routinely performed at the end of the fermentation runs. The viral clearance studies were performed with new and used chromatographic resins and column regeneration has been investigated.

In summary, the virus safety of DRL_RI has been sufficiently demonstrated and overall the adventitious agents safety evaluation is considered acceptable.

2.4.3.7. Biosimilarity

Ituxredi (DRL_RI) was developed as a biosimilar product to the reference medicinal product MabThera (rituximab) which is the EU sourced reference material and therefore the main comparator. Understanding of the reference product (RP) (US - Rituxan) and reference medicinal product (RMP) (EU - MabThera) was achieved by extensive structural and functional characterisation and structure-function relationships established experimentally, along with a survey of the scientific literature on rituximab to generate a Quality Target Product Profile (QTPP).

DRL_RI was well characterised considering the outcome of the reference products. Subsequently, criticality ranking for physicochemical and biological attributes was conducted and the numerical criticality ranking took account of clinical relevance for each attribute. A comprehensive similarity assessment was performed between DRL_RI, RP and RMP batches. Results obtained with RP are seen as supportive provided the data support comparability between RP (US-) and RMP (EU-) material. The criticality of each quality attribute has been ranked based on the severity and likelihood of clinical impact, and inherent precision of the assay used to measure the quality attribute. The overall risk classification is considered adequate The number of DRL_RI RP and RMP batches included in the biosimilarity exercise is sufficient. Batches used for side-by –side analysis, and batches used in Phase I and Phase III clinical trials are indicated.

Multiple analytical techniques were utilised to evaluate the overall amino acid composition and sequence of each protein, as well as the relative proportions of N- and C terminal variants. Overall, it is shown that DRL_RI, RP and RMP have identical amino acid sequence, and they are comparable with regard to different aspects of the primary structure analysis including the presence of the same N- and C-terminal variants and masses of the intact protein and subunits. The extinction coefficient experimentally determined for DRL_RI and RMP is identical. Overall, the results show that DRL_RI, RP and RMP have identical amino acid sequence and are comparable with regard to the primary structure. The secondary and tertiary structure of DRL_RI are shown to be similar to the RMP. Product related size impurities were evaluated in a comparative manner for DRL_RI, RP and RMP using orthogonal approaches and confirm comparability.

Post translational modification revealed only minor differences, which are either non-CQAs or the differences are so minor that no impact on biological function or clinical efficacy/safety is expected. A single site of glycosylation across the three products showed qualitatively similar glycan species with no unique species detected in DRL_RI.

The N-glycan profiles of DRL_RI and RMP are overlapping. Differences in charge variants were observed and identified. It was concluded that the identified modifications do not impact the biological activity of DRL_RI and are not considered clinically meaningful.

For assessment of effector functions, CDC and ADCC assays were performed. The functional assessment also included Fc binding (FcRn, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and C1q).

Regarding the observed differences, the Applicant provided the discussion and stressed the fact that the differences are not clinically meaningful as the comparable efficacy, pharmacodynamics (PD), safety, and immunogenicity in patients with moderate-to-severe rheumatoid arthritis in RI-01-003 Phase I clinical study was observed and in the RI-01-006 Phase III clinical study in low tumor burden follicular lymphoma patients efficacy equivalence between DRL_RI and MabThera was demonstrated and safety profile was comparable to that of MabThera. Thus, the issues are not further pursued as also an additional specification was implemented to better control the glycosylation pattern. Overall, the conclusion that DRL_RI and RMP are similar is agreed.

Overall, taking into account the totality of the data provided, biosimilarity of Ituxredi with MabThera is considered demonstrated from a quality point of view.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Several Major Objections concerning GMP-compliance (AS and FP), control strategy (AS), comparability (AS), manufacturing process development (FP), nitrosamine risk assessment (FP) were initially raised. These have been discussed in the respective sections above. Satisfactory responses and adequate supplemental information were provided and the Major Objections were considered resolved.

DRL_RI has been developed as biosimilar product to MabThera (rituximab), the reference medicinal product (RMP), which is the EU sourced reference material and therefore the main comparator. Understanding of the RP and the RMP was achieved by extensive structural and functional characterisation and structure-function relationships established experimentally, along with a survey of the scientific literature on rituximab to generate a QTPP. DRL_RI was well characterised considering the outcome of the reference products. Subsequently, criticality ranking for physicochemical and biological attributes was conducted and the numerical criticality ranking took account of clinical

relevance for each attribute. A comprehensive similarity assessment was performed between DRL_RI and RMP batches. The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its RMP. Overall, the conclusion that DRL_RI, RP, and RMP are similar is agreed. Regarding the observed differences the Applicant expanded the discussion but mainly stressed the fact that the differences are not clinically meaningful as the comparable efficacy, PD, safety, and immunogenicity in patients with moderate-to-severe rheumatoid arthritis in RI-01-003 Phase I clinical study was observed and in the RI-01-006 Phase III clinical study in low tumor burden follicular lymphoma patients efficacy equivalence between DRL_RI and MabThera was demonstrated and safety profile was comparable to that of MabThera.

Overall, taking into account the totality of the data provided, biosimilarity of Ituxredi with MabThera is considered demonstrated from a quality point of view.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ituxredi is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Ituxredi is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

DRL_RI, was developed as a proposed biosimilar to the U.S.-licensed RP and the EU approved RMP Mabthera. Similarity of DRL_RI is established based on the totality of evidence (TOE) generated using a stepwise approach to assess its similarity with rituximab RP with regard to analytical (structural and functional) characteristics, pharmacokinetic parameters, efficacy and safety. The non-clinical studies, in vitro functional characterization studies and the in vivo comparative toxicology study in cynomolgus monkeys, have been developed in accordance with the EMA guidelines as follows:

- EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues.
- EMA Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues.

Using a stepwise approach, the non-clinical development programme focused on the characterization of the physicochemical properties and functional activity of DRL_RI, the RMP and the RP in order to demonstrate similarity between DRL_RI and the reference products. To demonstrate pharmacological similarity, a battery of comparative biological in vitro studies were performed wherein DRL_RI was compared to RP and RMP with respect to Fab- and Fc-mediated activities

DRL has conducted a good laboratory practice (GLP)-compliant, comparative, once weekly repeat-dose toxicity study of DRL_RI, RP and RMP in Cynomolgus monkeys for 4 weeks. In this study, DRL has

evaluated the toxicity, pharmacokinetics, pharmacodynamics and immunogenicity of DRL_RI in comparison with RP and RMP.

The applicant should note that such studies are strongly discouraged from the European point of view and it is emphasized that the effort should be focussed on manufacturing process in order to develop the biosimilar as close as possibly to much the quality of the RMP. As stated in the EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, the in vitro assays may be more specific and sensitive than studies in animals and therefore these assays can be considered paramount in the nonclinical comparability exercise. Potential toxicities related to the nature of the product, e.g. MoA, antigen, are known. Other unidentified toxicities, e.g. due to impurities, should be very unlikely.

2.5.2. Pharmacology

DRL_RI was developed as biosimilar product to Rituxan (rituximab), the Reference Product (RP) and to MabThera (rituximab), the reference medicinal product (RMP), which is the EU sourced reference material and therefore the main comparator.

2.5.2.1. Primary pharmacodynamic studies

A comprehensive comparability exercise was conducted comparing DRL_RI to RP and RMP. Understanding of the RP or RMP was achieved by extensive structural and functional characterization and structure-function relationships established experimentally, along with a survey of the scientific literature on rituximab to generate a Quality Target Product Profile (QTPP). DRL_RI was well characterized considering the outcome of the reference products. Subsequently, criticality ranking for physicochemical and biological attributes was conducted and the numerical criticality ranking took account of clinical relevance for each attribute. A comprehensive similarity assessment was performed between DRL_RI, RP and RMP batches. Results obtained with RP are seen as supportive provided the data support comparability between RP (US-) and RMP (EU-) material. The criticality of each quality attribute has been ranked based on the severity and likelihood of clinical impact, and inherent precision of the assay used to measure the quality attribute. The overall risk classification is considered adequate. Batches used for side-by–side analysis, and batches used in Phase I and Phase III clinical trials are indicated.

Overall, the results show that DRL_RI, RP and RMP have identical amino acid sequence and are comparable with regard to the primary structure. The secondary and tertiary structure of DRL_RI are shown to be similar to the RMP. Product related size impurities were evaluated in a comparative manner for DRL_RI, RP and RMP using orthogonal approaches and confirm comparability. Post translational modification revealed only minor differences, e.g. C-terminal lysine and N-terminal glutamine, deamidation and oxidation, which are either non-CQAs or the differences are so minor that no impact on biological function or clinical E/S is expected. Differences in charged variants were observed and identified. It was concluded that the identified modifications do not impact the biological activity of DRL_RI and are not considered clinically meaningful as it was published by Schiestl, et al., 2011.

For the functional assessment of Fab mediated binding and functions, CD20 binding and induction of apoptosis were assessed using cell-based assays. CDC and ADCC activities were assessed using cell-based assays for DRL_RI, RMP and RP. Fc-mediated binding to C1q, FcγRIIIa, and FcRn implicated in effector functions or pharmacokinetics is similar between DRL_RI, RMP. Binding to other FcγRs [FcγRI,

FcγRIIa (R and H), FcγRIIb and FcγRIIIb] was also evaluated as part of the functional similarity assessment and the results demonstrate that the DRL_RI is considered similar to RMP and RP.

In the GLP 4-weeks repeat dose toxicology study, the pharmacodynamic activity of CD20 positive B-cells depletion was investigated. Treatment with DRL_RI resulted in comparable pharmacodynamics effects (B cell reduction) to those observed with the reference articles, Rituxan and MabThera. A marked reduction in CD40 positive B lymphocytes was observed in all treated animals within 4 hours after the first administration.

Overall, the analytical comparability assessment indicates that DRL_RI is to be considered similar to the RMP (EU-rituximab, MabThera).

2.5.3. Pharmacokinetics

Pharmacokinetic parameters were evaluated as part of the repeated dose toxicity study in Cynomolgus monkeys.

Determination of DRL_RI, Rituxan and MabThera in Cynomolgus Serum is done by MSD using electrochemiluminescence (ECL) as a detection technique.

The analytical procedure for the determination of RP, RMP and DRL_RI in Cynomolgus serum was successfully validated for a batch size of 48 samples. Validated parameters were identical for all three test samples (RP, RMP and DRL_RI). respectively. The method is considered suitable for determination of all three test samples in Cynomolgus monkey serum. The method for detection of ADAs in cynomolgus serum is based on the MSD platform including an acid dissociation step to release anti-rituximab antibodies.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No dedicated single dose toxicology studies were submitted.

2.5.4.2. Repeat dose toxicity

Table 1 Summary of the results of the comparative repeat dose toxicity study

Parameters Evaluated		Summary of Results
Toxicology	Mortality Clinical observations Body weights Food consumption Ophthalmoscopy Electrocardiography and blood pressures Haematology Bone marrow smears Clinical chemistry Urinalysis Organ weights Histopathology	No unscheduled deaths in any treatment group. No adverse clinical signs in any treatment group. Body weights stable with no effects of treatment noted in any group. No difference in food consumption between control and treatment groups No ophthalmic abnormalities detected in any treatment group. No biologically significant differences in heart rate or blood pressure between treatment groups. No consistent changes of toxicological significance in haematology or myelogram data; group mean white cell counts in males were lower in all three antibody treatment groups versus control. No consistent changes of toxicological significance in clinical chemistry. No effects of treatment on urinalysis. No effects of treatment on organ weights. In antibody treatment groups, minimal to slight lymphoid atrophy in spleen observed in all treated animals. Microscopic findings (fasciitis and phlebitis) at the injection site were consistent with mechanical trauma of continuous infusion and were recorded in all treatment groups.

Results of the repeated dose toxicity study in Cynomolgus monkeys indicate that the safety of DRL_RI, RP and RMP is comparable. No unexpected toxicological aspects were identified. The expected effect of B lymphocyte depletion and lymphoid atrophy in spleen was seen in all the treatment groups and are comparable.

2.5.4.3. Genotoxicity

Not applicable.

2.5.4.4. Carcinogenicity

Not applicable.

2.5.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted as they are not required for the non-clinical testing of biosimilars.

2.5.4.6. Toxicokinetic data

Comparative toxicokinetic evaluation was performed following once weekly intravenous (infusion) administration in the Cynomolgus monkey over a 4-week dosing period (dosing on Days 1, 8, 15, 22 and 29). Some animals developed positive immunological responses upon repeated administration and therefore results at week 4 are much more variable and some data are excluded from statistical summary. Most reliable results are obtained at week 1 and the data indicate that toxicokinetic parameters of DRL_RI, RMP and RP are comparable in male and female Cynomolgus Monkeys respectively.

2.5.4.7. Local tolerance

Microscopic findings at the injection site included fasciitis/fibrosis and phlebitis/periphlebitis and were recorded in both control and animals dosed with DRL_RI.

2.5.4.8. Other toxicity studies

Not applicable.

2.5.5. Ecotoxicity/environmental risk assessment

Rituximab is a monoclonal antibody, and is classified as a protein, consisting of naturally occurring amino acids therefore an Environmental Risk Assessment is not required for this medicinal product. Considering the nature of the product, it is not likely to have any impact on the environment. As rituximab drug product is an aqueous buffered protein- based preparation, it will degrade naturally in the environment and does not contain any ecologically harmful compounds that would pose any environmental risk.

2.5.6. Discussion on non-clinical aspects

A battery of comparative biological in vitro studies were performed to demonstrate pharmacological similarity wherein DRL_RI was compared to RP and RMP with respect to Fab-(CD20 binding and apoptosis induction) and Fc-mediated activities (FcRn, C1q, FcγRI, FcγIIa, FcγIIb, FcγIIIa, FcγIIIb binding as well as ADCC and CDC function). Overall, the analytical comparability assessment indicates that DRL_RI is considered similar to the RMP (EU-rituximab, MabThera). Comparative toxicokinetic evaluation was done in the Cynomolgus monkey.

The results observed in the Cynomolgus monkey studies have no correlation to the clinical outcomes (see clinical Pharmacology section) as DRL_RI demonstrated similarity in pharmacokinetics with RMP and RP, with comparable efficacy, PD, safety, and immunogenicity in patients with moderate-to-severe rheumatoid arthritis in RI-01-003 Phase I clinical study.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, rituximab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the nonclinical package is considered acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2 Overview of Clinical development programme

Descriptor	RI-01-003	RI-01-006	RI-01-007
Type of study	Pharmacokinetic, pharmacodynamic, safety, efficacy, immunogenicity	Efficacy, safety, immunogenicity	Safety and immunogenicity after single transition
Study design	Double-blind, randomised, parallel-group study	Double-blind, randomised, active-controlled, parallel-group, equivalence, Phase 3 study	Randomised, double-blind, parallel-group, multicenter, Phase 3
Indication	Moderate to severe active, seropositive RA	Stage II-IV, CD20-positive, LTB-FL	Active rheumatoid arthritis
Treatment regimen	Subjects were randomly assigned in a 1:1:1 ratio to receive one dose of 1000 mg of DRL_RI, Rituxan, or MabThera on Day 1 and on Day 15 by i.v. infusion	Subjects were randomised in a 1:1 ratio to receive DRL_RI or MabThera as an intravenous (i.v) infusion, at a dose of 375 mg/m^2 of BSA, every week for 4 weeks as induction treatment followed by maintenance treatment consisting of an i.v infusion every 8 weeks up to Week 36	Subjects were randomly assigned in a 1:1 ratio to receive either two 1000-mg IV infusions of DRL_RI (Arm A) or Rituxan/MabThera (Arm B) on Day 1 and Day 15
Duration of study	58 weeks (Part 1: 30 weeks [6 weeks of screening period and 24 weeks of treatment period] Part 2: 28 weeks of follow-up period)	57 weeks (5 weeks of screening period, 36 weeks of treatment period, 16 weeks of follow-up period)	28 weeks (2 weeks of screening period, 2 weeks of treatment period, 24 weeks of follow-up period)
Subjects enrolled	276 subjects (DRL_RI =91, Rituxan =92, MabThera =93)	317 subjects (DRL_RI = 162 and MabThera = 155)	140 subjects (DRL_RI = 70 and Rituxan or MabThera = 70)

Descriptor	RI-01-003	RI-01-006	RI-01-007
Population (inclusion criteria)	Male or female subjects aged between 18 and 65 years with diagnosis of RA, according to ACR criteria (1987), of at least 6 months duration and tender joint count ≥6 and swollen joint count ≥6 at randomisation. Subjects receiving oral or parenteral MTX at a dose of 15 to 25 mg per week when given alone or 10 to 25 mg per week in combination with additional non-biologic DMARD(s) for at least 6 months and on stable dose for at least 3 months. Evidence of at least moderate disease activity defined as all of the below: • Serum CRP level ≥1 × upper limit of normal (ULN) or erythrocyte sedimentation rate (ESR) ≥28 mm • Positive rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibodies • DAS28-CRP >3.2 despite stabilised therapy for at least the last 3 months for MTX and 4 weeks for additional non-MTX DMARDs	Male or female subjects aged ≥18 years with histologically confirmed Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF based criteria. Subjects had Ann Arbor Stage II to IV and ECOG status of 0 to 1. Subject had at least 1 measurable tumour mass in 2 dimensions, and the mass was nodal lesion >15 mm in the longest dimension; or nodal lesion >10 mm to ≤15 mm in the longest dimension; and >10 mm in the shortest dimension; or extra-nodal lesion with both long and short dimensions ≥10 mm	Male or female subjects aged ≥18 years with diagnosis of active RA who were eligible for the subsequent treatment course with Rituxan or MabThera according to the clinical judgement of the Investigator. Documented evidence that subjects received at least 1 full course comprising two 1000 mg infusions of either Rituxan at least 16 weeks prior or MabThera at least 24 weeks prior to the day of randomisation visit. Subjects receiving a stable dose of weekly MTX for at least 4 weeks prior to randomisation (between 7.5 mg and 25 mg) and folic acid (at least 5 mg per week)

Descriptor	RI-01-003	RI-01-006	RI-01-007
Primary endpoints	• Area under the concentration-time curve (AUC) from time 0 to 336 hours ($AUC_{0\text{-}14\ days}$) after first dose and from time 0 to infinity ($AUC_{0\text{-}\infty}$) over the entire course of therapy (two doses) from Day 1 through Week 16 • Area under concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$) (second dose).	• BORR, defined as the proportion of subjects in each treatment group that achieved a best overall response of either CR, CRu or PR up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma	• Incidence of anti-drug antibodies (ADA), including titre and neutralising antibodies (NAb) • Incidence of treatment-emergent adverse events and serious adverse events • Incidence of anaphylactic reactions, hypersensitivity • Reactions, and infusion-related reactions (IRRs)
Status of CSR	Final CSR Part 1 (up to 24 weeks) and Final CSR Part 2 (Week 24 through 52 weeks)	Primary CSR (up to 28 weeks)	Final CSR (up to 26 weeks)

Abbreviations: BOR = best overall response` BORR = best overall response rate; CD = cluster of differentiation; CR = complete response; CRP = C-reactive protein; CRu = unconfirmed complete response; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; DMARD = disease-modifying antirheumatic drug; ECOG = Eastern Cooperative Oncology Group; ESR = erythrocyte sedimentation rate; GELF = Groupe d'Etude des Lymphomes Folliculaires; IQR = interquartile range; i.v. = intravenous; LTB-FL = low tumour burden follicular lymphoma; MTX = methotrexate; PR = partial response; QoL = quality of life; RA= rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit normal.

2.6.2. Clinical pharmacology

Clinical pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of DRL_RI, rituximab-EU (MabThera), and rituximab-US (Rituxan) were evaluated in a PK similarity study (study RI-01-003 in RA patients). Supportive data were derived from a comparative efficacy, safety, PD, Pop PK and immunogenicity study (study PI-01-006 in LT-BFL patients) and from a "single transition trial" (study PI-01-007). In this transition study, RA patients - after having received at least 1 full course of treatment with either Rituxan or MabThera - either switched to the DRL_RI biosimilar or remained on their initial treatment with either Rituxan or MabThera).

Table 3 List of clinical studies used for evaluation of clinical pharmacology

Type of Study / Study Number	Study Design	Subjects	Dosing regimen	Objectives
RI-01-003	**Part 1: 3-way PK similarity**; Double-blind, randomised, 3-arm, parallel-group study designed to compare PK profiles of DRL_RI (n=91), Rituxan (n=92), and MabThera (n=93) **Part 2: Recovery and follow up: during this period safety and immunogenicity were assessed** (main study period; n = 254, extension period; n = 240)	Adult patients with moderate-severe active RA	Two – 1000 mg i.v infusions separated by 2 weeks	**Primary:** • To compare the plasma PK profile of DRL_RI, MabThera, and Rituxan in patients with RA over 1 course of therapy, consisting of 2 doses administered 2 weeks apart. **Secondary:** • To compare the DAS28-CRP scores over the course of 24 weeks as a PD measure of DRL_RI, MabThera, and Rituxan; • To evaluate the extent and kinetics of the depletion of peripheral B-cells as an additional PD measure of DRL_RI, MabThera, and Rituxan; • To assess the efficacy, safety including B-cell recovery, tolerability, and immunogenicity of DRL_RI, MabThera, and Rituxan. **Exploratory:** • To explore the relationship between study drug administration and risk of reactivation of latent tuberculosis infection in patients with RA.
Phase 3 RI-01-006	**Equivalent efficacy**: Double-blind, randomised, parallel-group study designed to compare efficacy, safety, and immunogenicity of DRL_RI (n=162) to MabThera (n=155)	Adult patients with Stage II-IV, CD20+ LTB-FL	375 mg/m^2 weekly i.v infusion for 4 weeks (induction) followed by i.v infusion every 8 weeks starting at Week 12 until Week 36 (maintenance)	**Primary:** • To demonstrate the equivalent efficacy of DRL_RI and MabThera in subjects with B-lymphocyte antigen CD20-positive, LTB-FL, as measured by ORR up to Week 28, evaluated in accordance with published response criteria for malignant lymphoma. **Secondary:** • To compare the ORR at Week 12 and Week 28, CR at Week 28, CR as a best response up to week 28, DOR, PFS and OS of DRL_RI with MabThera in subjects with CD20-positive, LTB-FL; • To compare the safety, tolerability, and immunogenicity of DRL_RI with MabThera in subjects with CD20-positive, LTB-FL. **Exploratory:** • To compare ORR evaluated in accordance with the Lugano criteria in subjects with CD20-positive, LTB-FL treated with either DRL_RI or MabThera; • To explore the PK parameters of DRL_RI and MabThera, using a population-PK modelling approach; • To explore the PD parameters of DRL_RI and MabThera.
Phase 3 transition RI-01-007	**Switching**: Double-blind, randomised, parallel-group study to assess the immunogenicity and safety of transitioning subjects to DRL_RI (n = 70) or continued treatment with the Rituxan (n = 22) or MabThera (n = 48)	Adult RA patients who are already on treatment with Rituxan or MabThera	Two – 1000 mg i.v infusions separated by 2 weeks	• To assess the immunogenicity of transitioning subjects with RA to DRL_RI (biosimilar rituximab) from Rituxan/MabThera to continued treatment with Rituxan/MabThera. • To assess the safety of transitioning subjects with RA to DRL_RI from Rituxan/MabThera to continued treatment with Rituxan/MabThera.

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics; RA = rheumatoid arthritis; LTB-FL = low tumour burden follicular lymphoma; i.v. = intravenous; ORR = overall response rate; CR = complete response; DOR = duration of response; PFS = progression-free survival. OS = overall survival; DAS28-CRP = disease activity score 28-C-reactive protein.

2.6.2.1. Pharmacokinetics

PK similarity was evaluated in study RI-01-003. This was a randomised, multicentre, double-blind, parallel 3-way equivalence study comparing DRL_RI with MabThera and Rituxan in combination with non-biological disease-modifying antirheumatic drugs (DMARDs) in patients with active RA. This study evaluated PK, pharmacodynamics, efficacy, immunogenicity, and safety at Week 24.

The study was conducted in 2 parts, a treatment and evaluation period (Part 1), and a recovery and follow-up period where all patients were followed up for safety and immunogenicity through Week 52 (Part 2).

Data for Part 1 of the study included complete PK analysis, the B-cell and DAS28-CRP based PD analysis, efficacy, safety and tolerability, and immunogenicity up to Week 24.

Data for Part 2 included B-cell recovery results, additional safety data, and immunogenicity results post-Week 24 up to Week 52.

The applicant argues that the difference in protein concentration did not affect efficacy or safety and did not lead to different exposure based on the fact that efficacy and clinical outcomes of DRL_RI are similar and DRL_RI demonstrated similarity in pharmacokinetics. Considering that the protein concentration of the DRL_RI batches used in the clinical trials are within the originators range, these results are not unexpected, but it needs to be ensured that a potential lower exposure does indeed not impact efficacy and safety if batches are being used with a protein content lower than the minimum content measured in originator batches. The applicant attributes the slight differences seen between DRL_RI and MabThera in to the inter-subject variability observed in the study, which might be the case as the protein concentration of the DRL_RI batches used in the clinical trials matches the originators range. It is noted that the 91% CIs for the Geometric Mean Ratio between the primary parameters and secondary parameters were contained within the predefined 80.00% to 125.00% bioequivalence limits.

Primary objective:

- To compare the plasma PK profile of DRL_RI, MabThera, and Rituxan in patients with RA over 1 course of therapy, consisting of 2 doses administered 2 weeks apart.

Secondary Objectives:

- To compare the DAS28-CRP over the course of 24 weeks as a PD measure.

- To evaluate the extent and kinetics of the depletion of peripheral B-cells as an additional PD measure.

- To assess the efficacy, safety including B-cell recovery, tolerability, and immunogenicity of DRL_RI, MabThera, and Rituxan.

Exploratory objective:

- To explore the relationship between study drug administration and risk of reactivation of latent tuberculosis infection in patients with RA.

Supportive data were derived from studies RI-01-006 (Phase 3 comparative efficacy study) and RI-01-007 (single transition trial in RA patients).

Bioanalytical methods

The scope of the PK evaluations during clinical development was as follows: Study RI-01-003 in subjects with RA was the pivotal study demonstrating PK similarity between DRL_RI, MabThera, and Rituxan. In Study RI-01-006 immunogenicity and PK of DRL_RI were demonstrated to be similar to

that of MabThera in subjects with previously untreated, stage II-IV, CD20-positive LTB-FL. In Study RI-01-007, the time-matched rituximab concentrations (TMRC) values at all evaluated times appeared comparable between both treatment groups. In addition, the circulating rituximab concentrations did not interfere in ADA interpretation in both treatment groups.

Bioanalytical methods applied during the clinical developments included an enzyme-linked immunosorbent assay (ELISA) for measuring the concentrations of rituximab in human plasma, an affinity capture elution (ACE) based immunoassay for the detection of anti-drug (rituximab) antibodies (ADA) in human plasma, a cell-based assay for the detection of neutralizing antibodies (NAb) in human plasma and a Flow Cytometry Assay to evaluate B cells depletion.

A report was submitted to demonstrate that the CD19+ B Cell flow cytometry assay in Cyto-Chex Blood Collection Tubes (BCT) is not being affected by Rheumatoid factor (RF) in RA patients. The data set demonstrates that the pre-defined acceptance criteria were for intra-assay precision and recovery for normal, RFhi and RFlo donor samples, thus supporting the suitability of the assay for evaluation of B-cells in whole blood from healthy donors and RA patients. The method for analysis of TBNK (T-, B-, and NK lymphocytes) on the FACS Canto II is suitable in both laboratories, Breda and Lancaster.

The ELISA method for the quantification of DRL_RI, MabThera, and Rituxan in K3EDTA Rheumatoid Arthritis (RA) human patient plasma involves coating plates with monoclonal rat anti-rituximab antibodies to capture rituximab in human plasma, followed by detection with biotinylated goat anti-human IgG (Fc Specific) antibody. In a second step, streptavidin horseradish peroxidase was bound to the biotinylated goat anti-human IgG (Fc-specific) antibody. The addition of substrate results in the development of colour that was measured at 450 nm. The method has been validated in terms of system suitability, assay accuracy and precision, linearity, selectivity, and sample stability. Data indicate the method is suitable for the intended use. Results of a study conducted to partially validate a method, utilizing new lots of test article, for the quantification of Rituxan, MabThera, and DRL_RI in human plasma from rheumatoid arthritis patients at Labcorp Early Development Laboratories Inc., is provided. It was concluded that that the method described is suitable for the determination of DRL_RI, MabThera, and Rituxan Human Plasma from Rheumatoid Arthritis Patients, utilizing new lots of test article, and has been successfully validated. The method for the quantitation of rituximab in Follicular Lymphoma K3EDTA human plasma was considered sufficiently validated and found suitable for the intend use. During validation it turned out that haemoglobin levels due to haemolysis may interfere with selectivity of the assays and thus, samples should be closely monitored for signs of haemolysis.

In studies RI-01-003, RI-01-006 and RI-01-007, analysis of ADA samples followed a tiered approach of screening, confirmatory, and titre determination. Samples were screened for ADA and a positive ADA status was confirmed by a second assay. Samples that were confirmed positive for ADA were further tested for titre and NAb status using validated assays. An overview of the strategy used to determine sample ADA status was provided. The detection of ADAs in human plasma was achieved using an affinity capture elution (ACE) immunoassay. The ELISA method for detection of anti-Rituxan, anti-MabThera, anti-DRL_RI antibodies in human plasma includes an acid dissociation step. The free anti-drug antibodies are captured on a solid-phase by drug coated to an ELISA plate. Following a washing step, the bound anti-drug antibodies are subsequently released and transferred to a fresh plate where these antibodies are detected using biotin-labelled F(ab)2 fragments of DRL_RI, which is acceptable for all three test samples. The positive control antibody used in the method was rat-anti-rituximab. The method was evaluated for assay cut-points (screening and confirmation), titre cut-point, sensitivity, drug tolerance, selectivity / matrix interference, intra- and inter-assay precision, hook effect and stability. The assay sensitivity in the absence of drug was determined as 4.605 ng/mL. With regard to drug tolerance at the lowest concentration of positive control tested (62.5 ng/mL) a positive response was detected in the presence of 50 µg/mL drug product. Positive control at 125 ng/mL can be detected in the presence of 100 µg/mL drug product. Assay sensitivity and Drug tolerance are considered

sufficient. Intra-and Interassay precision for both screening and confirmatory assay are acceptable. Overall it is agreed that that the method is suitable for the detection, confirmation and quantitation of antibodies to rituximab in Rheumatoid Arthritis Human Plasma. Validation data demonstrate the method to detect antibodies to Rituximab in human Follicular Lymphoma K3EDTA plasma is suitable. Similarly, as for method for the Quantitation of rituximab in Follicular Lymphoma K3EDTA Human Plasma, selectivity criteria were not met in haemolytic FL plasma and it is requested that clinical study samples appearing haemolytic should be clearly documented.

The method principle for identification of neutralizing antibodies to rituximab is complement dependent cytotoxicity (CDC). The method involves acid-dissociation and then a solid phase extraction of antibodies from controls and samples using magnetic beads that are coated with DRL_RI. The anti-Rituximab antibodies eluted from controls and samples (if present) are incubated with cells in the absence and presence of a fixed concentration of DRL_RI, in addition to complement obtained from baby rabbit plasma. In the presence of Rituximab, CDC occurs. If samples and controls contain anti-Rituximab neutralizing antibodies, these neutralizing antibodies will neutralize Rituximab-mediated CDC. The neutralizing activity level of anti-Rituximab neutralizing antibodies correlate to cell viability measured by a fluorescence-based viability assay. The results of the validation study of the method for detection and identification of rituximab neutralizing antibodies in human plasma demonstrate that the method is sufficiently sensitive and precise. Drug tolerance is acceptable for all three test samples although it was noted that higher % neutralization values calculated at PC1000 (1000 ng/mL) using DRL's Rituximab were noticed compared to MabThera and Rituxan. It was concluded that this could be due to the intrinsic nature of a bead based assay which is not considered a well justified discussion but overall it is agreed that this difference does not impact the overall validation outcome. The cell-based method used in clinical study RI-01-007 to detect anti-rituximab neutralising antibodies is the same as the one used in the Study RI-01-003, but was validated in a different contract lab (Syneos). The validation data confirm that the assay is suitable for the intended use. Again, a difference in drug tolerance was observed but this time for MabThera indicating that these minor differences can be neglected and do not impact the overall validation outcome which is considered sufficient. In Study RI-01-006 was conducted to demonstrate comparable immunogenicity and PK of DRL_RI and MabThera in subjects with previously untreated, stage II-IV, CD20-positive LTB-FL The method for the detection of anti-rituximab neutralizing antibodies in human follicular lymphoma K3EDTA plasma is considered suitable for its intended use.

Generally, the validation data demonstrate that all methods are suitable for their intended use. The Applicant has provided sufficient explanation for not performing parallelism analyses. Also the results for matrix effect as a part of selectivity assessment were provided.

The Applicant has provided the bioanalytical results for the determination of the DRL_RI, Rituxan, and MabThera, in support of clinical study RI-01-003. The bioanalysis was performed for a total 5760 samples, and was found to be acceptable according to the within ranges accuracy and precession for calibrators, QC samples and ISR results.

Moreover, the Applicant has submitted the results of the bioanalysis for determination of ADA in support of clinical study RI-01-003. A total 1299 samples were analysed for ADA form which 248 samples were initially screened positive. From them, 93 samples were confirmed positive and tested in the titre assay. Finally, 47 samples were reported with a titre result. ADA analysis appear to be valid.

The bioanalytical report for Detection of neutralizing antibodies to rituximab in human K3EDTA plasma was submitted in support of protocol RI-01-007. ADA-positive samples were further analysed for NAb presence.

<u>Population PK model for rituximab in RA and TLB-FL patients</u>

A population PK model was developed which was based on PK data from studies RI-01-003 and RI-01-006. In total, 6185 PK concentration measurements from 351 patients were included in the analysis. The final PK model was a two-compartment model with first-order elimination from the central compartment with the mechanistic covariates WT on CL- and V-terms. Sex was implemented in addition to WT for the allometric scaling. Baseline DAS28-CRP was included as a covariate on CL. IIV terms were supported on Vc, CL and Vp, including a correlation between Vc and CL. The RUV for PK was described by an additive model on the log-scale including an IIV term on RUV.

Table 4 Parameter estimates of the final population PK model

	Final PK model			
Run		33		
OFV		−12705.32		
Condition number		14.51		
	Final PK model			
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL	(mL/day)	282	2.05	
V_c	(mL)	2670	1.33	
Q	(mL/day)	757	1.83	
V_p	(mL)	2530	1.67	
WT on CL and Q		0.508	8.19	
WT on V_c and V_p		0.468	5.61	
Second dose on CL[a]		-0.0847	16.0	
Subsequent doses on CL[b]		-0.284	8.48	
Sex on the allometric scaling		0.421	16.6	
DAS28-CRPB on WT effect		0.110	22.5	
IIV CL	(CV)	0.277	3.82	1.18
IIV V_c	(CV)	0.190	4.33	5.17
Corr CL-V_c		0.467	6.80	
IIV V_p	(CV)	0.190	6.10	16
IIV RUV	(CV)	0.498	3.99	0
RUV	(CV)	0.159	3.29	0.893

[a]Represents the fractional decrease in CL after administration of the second dose in study study RI-01-003.
[b]Represents the fractional decrease in CL after administration of subsequent doses in study study RI-01-006.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.

Visual predictive check (VPC) as well as goodness of fit (GOF) plots for studies RI-01-003 and RI-01-006 have been provided.

Figure 2 VPC plot study RI-01-003

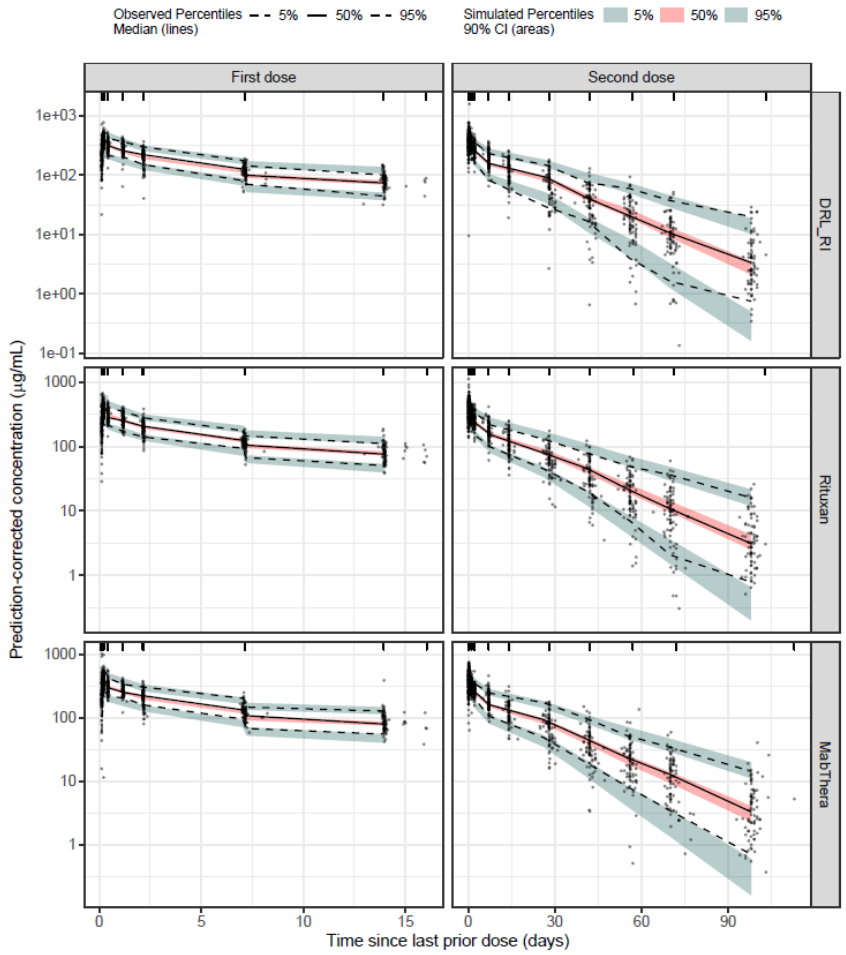


Figure 3 VPC plot study RI-01-006

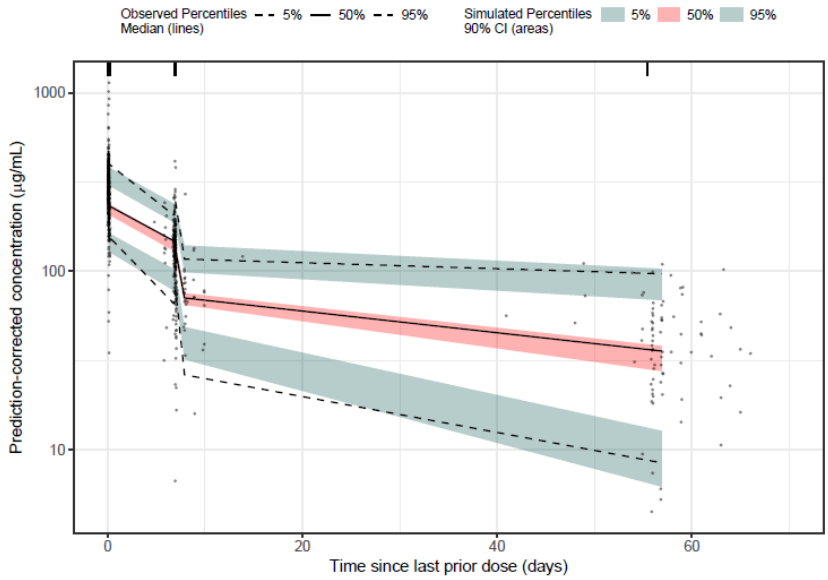
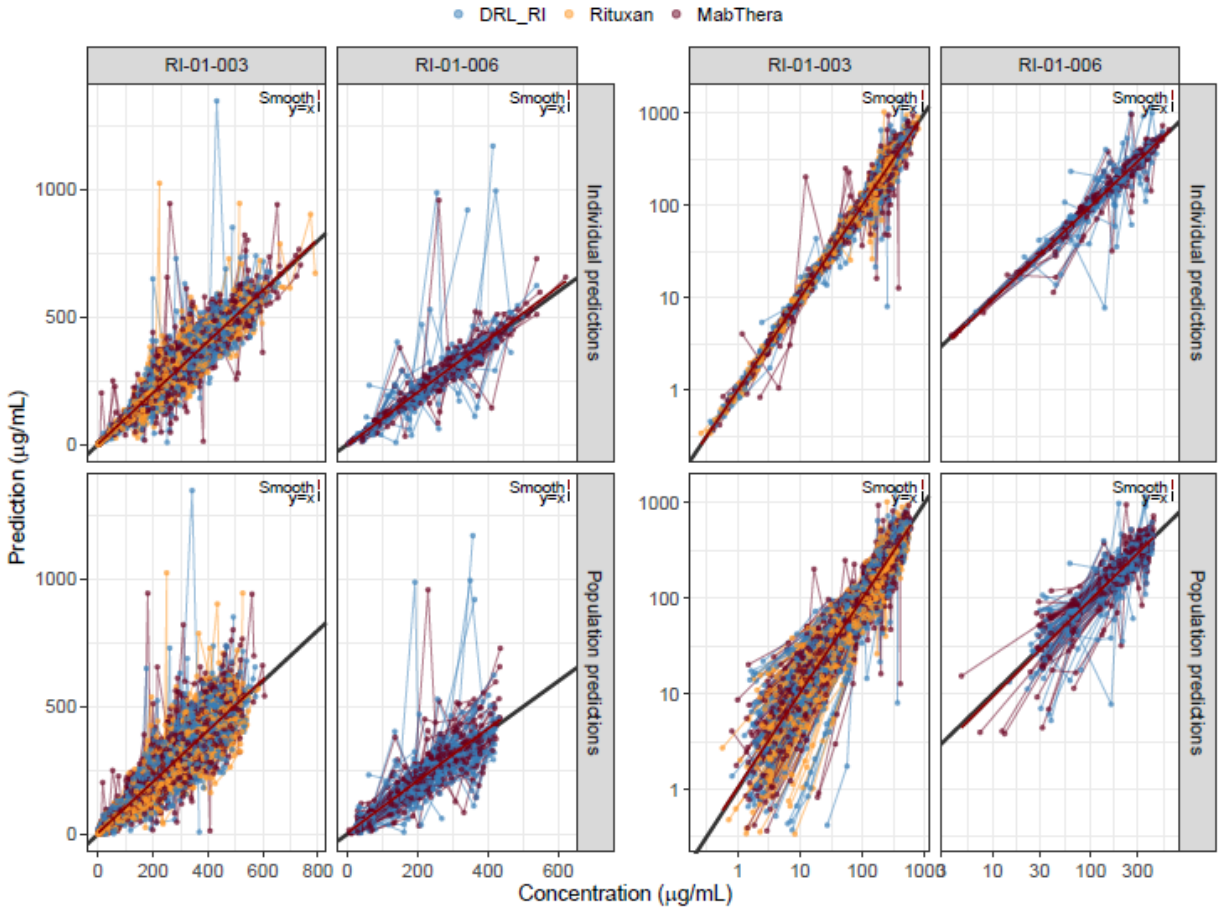


Figure 4 GOF plots



Statistical methods

The primary PK parameters to be used for statistical comparisons in the PK similarity study RI-01-003 were AUC 0-14 days after first dose and, AUC 0-inf over the entire course of therapy (two doses) from Day 1 through Week 16, and AUC 0-t (second dose).

A minimum total of 246 patients would be required for the analysis of the primary PK endpoints. The sample size was based on an anticipated 43% coefficient of variation (CV). Assuming a true geometric mean ratio (GMR) between 0.95 and 1.05, 82 patients per group (246 in total) would provide at least 83% power for the geometric mean treatment ratio 91 % confidence interval (CI) to be between 80% and 125% for each pairwise comparison. A further adjustment of 10 patients per group was made to account for an estimated 10% rate of dropout, resulting in the initial enrolment of 92 patients per group or 276 patients in total.

A blinded sample size re-estimation procedure was conducted when approximately 40% of the patients have been enrolled and completed 16 weeks in the study (internal pilot study). The blinded sample size re-estimation procedure was based on the overall variability of all combined treatments observed for Cmax and AUC0-∞, taking the maximum of the CV observed for each endpoint. If the overall variability was larger than what was initially assumed, the final sample size would be recalculated based on this variability and a power level for the pairwise comparisons set at 85%. To take the potential α-inflation into account, a nominal alpha level of 0.045 (leading to a 91% CI) was used in order to control the type 1 error rate at the 5% significance level.

The three parameters were analysed using an analysis of variance (ANOVA) model with treatment, gender and region (India, Ukraine) as covariables, using the natural logarithms of the three PK parameters as outcome variables.

Pharmacokinetic equivalence of each pair of study treatments (DRL_RI/Rituxan, DRL_RI/MabThera, Rituxan/MabThera) was concluded if the 91 % CIs for the GMR for AUC 0-14 days after first dose, AUC0-inf, and AUC 0-t after the second dose were contained within 80% to 125%.

The 91 % CIs for the test/reference GMR of Cmax after the second dose was also reported.

All eligible patients were randomly assigned in a 1:1:1 ratio to 1 of the 3 treatments (DRL_RI 1000 mg IV infusion, Rituxan 1000 mg IV infusion, MabThera 1000 mg IV infusion). Patients were to be randomized to treatment via a stratified block randomization. Randomization was to be stratified by gender. If the study is conducted outside India, then regions (countries/subcontinents) were also to be considered as a stratification factor for randomization. During the study conduct, a total of 13 patients were force randomized, which is a process of allocation of study drug to a group of patients due to lack of availability of kits of a specific treatment arm. Adequate IP/RMP kits were not available to have the kits of all 3 treatment arms at all sites at any given point, hence auto resupply was stopped and manual resupply was adopted. Forced randomization is an automatic feature that led to assignment of the patient to the next treatment arm based on the randomization sequence and arm of kit available at the site and ensured to maintain the blind.

Forced randomization was initiated on 01 Jan 2015 and deactivated on 25 Sep 2015 to restrict the overall percentage of forced randomized patients to less than 5% of the total of 276 patients that were randomized. The first patient was force randomized on 1 Apr 2015 and last patient on 22 Sep 2015. Since the proportion of force randomized patients were relatively low, no adverse impact on PK, PD, efficacy, safety, and immunogenicity results were implicated which were further described by additional sensitivity analysis.

Additional sensitivity analyses were performed by including and excluding forced randomized patients.

For analyses based on PK, patients were classified according to the actual treatment received. The PK Population was defined as including all patients who received both doses of study drug (on Day 1 and Day 15) and had sufficient plasma samples for PK assessments to establish profile. The ADA positive patients were excluded from the PK Population.

The following changes were done on top of the PK Population as defined in statistical analysis plan (SAP) and finalized during the /in blinded data review meeting (BDRM):

• Sensitivity Analysis 1 PK Population: This population included all patients having confirmed ADA positive results and forced randomized patients;

• Sensitivity Analysis 2 PK Population: This population excluded both forced randomized patients and patients having confirmed ADA positive results.

PK results

Data are presented from the PK equivalence study RI-01-003 that compared the full PK profile of DRL_RI with MabThera and Rituxan in a 3-way comparison in RA subjects after a 1000 mg infusion administered on Day 1 followed by a 1000 mg infusion on Day 15.

PK parameters were assessed in the PK population. The PK population included all patients who received both doses of study drug and had sufficient plasma samples for PK assessments. Patients with relevant protocol violations thought to affect the evaluation of PK similarity (such as IRR requiring infusion interruption or incomplete study drug administration) or with confirmed antibodies to study drug were not included in the PK population.

The primary PK endpoints AUC0-14 days, first infusion, AUC0-inf, entire course, and AUC0-t, second infusion are considered similar among the 3 study drugs. Ratios of adjusted geometric means and corresponding 91% CIs for the primary comparisons are provided. For the PK similarity comparisons of DRL_RI to each of the RPs (rituximab-EU and rituximab-US), the 91% CIs for the test-to reference ratios of AUC0-14 days, AUC0-inf and AUC0-t were within the bioequivalence acceptance criteria of 80.00% to 125.00%.

This was also true for the secondary PK endpoints, Cmax first infusion, Cmax second infusion, and AUC0-t, entire course.

Table 5 Statistical comparison of key study drug PK properties (PK population excluding ADA positive patients, n=230)

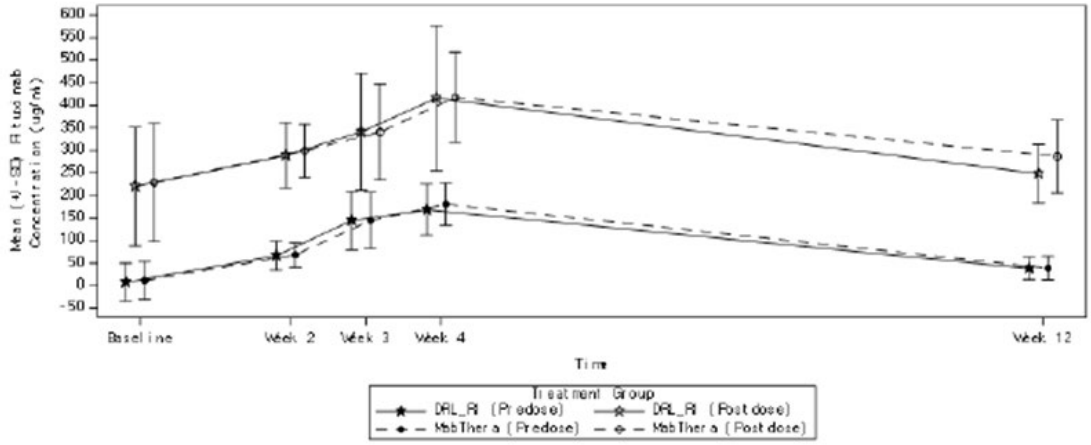
Parameter (Unit)	Treatment	n	GLS Mean	Statistical Comparisons GLS Mean Ratio (91% CI) (%)		
				DRL_RI / Rituxan	DRL_RI / MabThera	Rituxan / MabThera
PK Population – Primary Endpoints						
$AUC_{0\text{-}14\ days,\ first\ infusion}$ (µg*h/mL)	DRL_RI	74	42380	100.80 (94.62; 107.38)	95.45 (89.60; 101.68)	94.69 (88.85; 100.92)
	Rituxan	72	42040			
	MabThera	72	44400			
$AUC_{0\text{-}inf,\ entire\ course}$ (µg*h/mL)	DRL_RI	73	162000	100.37 (92.30; 109.14)	93.58 (85.98; 101.85)	93.24 (85.62; 101.54)
	Rituxan	71	161500			
	MabThera	68	173200			
$AUC_{0\text{-}t,\ second\ infusion}$ (µg*h/mL)	DRL_RI	76	118100	101.55 (92.60; 111.36)	94.83 (86.52; 103.93)	93.38 (85.08; 102.50)
	Rituxan	71	116300			
	MabThera	73	124600			
PK Population – Secondary Endpoints						
$AUC_{0\text{-}t,\ entire\ course}$ (µg*h/mL)	DRL_RI	71	160600	100.66 (92.71; 109.30)	94.24 (86.71; 102.42)	93.61 (86.11; 101.77)
	Rituxan	70	159600			
	MabThera	67	170400			
$C_{max,\ first\ infusion}$ (µg/mL)	DRL_RI	74	348.229	105.31 (98.70; 112.37)	100.25 (93.95; 106.97)	95.19 (89.17; 101.61)
	Rituxan	72	330.659			
	MabThera	72	347.370			
$C_{max,\ second\ infusion}$ (µg/mL)	DRL_RI	78	420.740	104.68 (98.17; 111.63)	102.26 (95.94; 109.00)	97.69 (91.53; 104.26)
	Rituxan	72	401.926			
	MabThera	74	411.447			

Abbreviations: CI = Confidence interval; GLS = Geometric least-squares; PK = Pharmacokinetic; n = Number of patients with available data.
Results based on an ANOVA model with treatment (DRL_RI, MabThera, and Rituxan), region and gender being considered as fixed effects. The values are back transformed from the log scale. Patients with a confirmed ADA positive result were excluded from the PK population.

Sensitivity analyses for the primary endpoints were performed in two populations: in the PK population including ADA positive patients, and in the PK population excluding ADA positive and forced randomization patients. They were supportive for the primary analysis in the original PK population, since their 91% CIs for the ratios of GM met the acceptance criteria of 80.00 to 125.00%.

Supporting PK data (Ctrough levels) were provided from LTB-FL patients in study RI-01-006 as part of exploratory endpoints. Both DRL_RI and MabThera had similar mean concentrations prior to each collection time point.

Figure 5 Arithmetic mean plasma concentration profiles (PK analysis set)



Abbreviations: DRL_RI = Dr Reddy's rituximab; SD = standard deviation.

In study RI-01-003, in patients with RA, the Vd (volume of distribution) of DRL_RI, Rituxan, and MabThera were evaluated. No significant differences were observed in the Geo Mean of Vd (5.69, 5.76, and 5.55L – for DRL_RI, Rituxan, and MabThera). The observed range of Vd for DRL_RI (3.36-19.2L) was higher than for MabThera (2.41-10.9L) and higher than reported in the SmPC for MabThera (range 1.7 – 7.51L). The Applicant provided an additional analysis of the data on Vd. It was revealed that in the case of individual subjects who took DRL_RI, unexpectedly high Vd was observed. Following the reanalysis of the data, excluding this subject, the Vd appears to be comparable between treatment arms. However, the Applicant did not present a rule that allows the identification of extreme results. There were no significant protocol deviations reported for the subject displaying this outlier. Baseline albumin, protein levels, liver enzymes, and serum creatinine values were within the normal reference range. Therefore, the probable reason for such a high Vd remains unclear. However, the phenomenon appears to be random.

In the study, the T1/2 (elimination half-life) and CL (clearance) of DRL_RI, Rituxan, and MabThera were evaluated. The Geo Means of T1/2 were found to be 374, 378, and 391 hours, respectively, for each medication. The mean values for the Cl were 0.254, 0.254, and 0.238 L/day for DRL_RI, Rituxan, and MabThera, respectively.

However, it was noted that the GCV% of T1/2 for DRL_RI was higher than the EU reference (MabThera) at 30.1% vs 23.9%, with an unexpectedly short minimum T1/2 of 119h for DRL_RI (PK Population excluding ADA positive patients). The applicant conducted an additional analysis of data concerning the occurrence of extreme results that influenced the determination of half-life. It was demonstrated that extreme results were present in each examined group (both the test rituximab and the two reference drugs). It should be noted that extreme results were more frequently observed for DRL_RI (DRL_RI 7, Rituxan 3, MabThera 2). One of the extreme results involved an individual with a very short half-life. An analysis of factors that could have influenced this result was conducted; however, no significant cause for this phenomenon was identified. The ADA status was negative. The cause of the very short half-life was not explained; however, the phenomenon appears to be random.

Table 6: Summary Statistics for Key Study Drug PK Parameters (PK Population Excluding ADA Positive n=230)

Parameter	Statistic	DRL_RI (N=79)	Rituxan (N=73)	MabThera (N=78)
	GCV%	32.3	33.2	29.5
	Min	62900	82900	108000
	Median	193000	193000	198000
	Max	310000	355000	343000
$t_{1/2}$ (h)	n	79	73	78
	Geo Mean	374	378	391
	GCV%	30.1	25.0	23.9
	Min	119	228	233
	Median	366	369	387
	Max	640	616	627
Clearance (L/day)	n	73	71	68
	Geo Mean	0.254	0.254	0.238
	GCV%	33.2	33.9	30.0
	Min	0.147	0.131	0.135
	Median	0.253	0.248	0.241
	Max	0.759	0.577	0.444
Volume of distribution (L)	n	73	71	68
	Geo Mean	5.69	5.76	5.55
	GCV%	26.3	23.1	26.4
	Min	3.36	3.76	2.41
	Median	5.44	5.57	5.43
	Max	19.2	11.3	10.9

Abbreviations: GCV%: Geometric coefficient of variation in percent; Geo: Geometric; Max: Maximum; Min: Minimum; PK: Pharmacokinetic
Note: AUC_{0-t} for a PK profile were excluded from population summaries and analyses if t_{last} was missing or considered to be unreliable. However, if λ_z was still accurately estimable for the profile, $AUC_{0-\infty}$ and related parameters were reported. Since $AUC_{0-14\ days}$ and $AUC_{0-t,\ first\ infusion}$ are equivalent parameters the latter is omitted from the in-text tables.
Source: Table 14.2.2.1.1, Table 14.2.2.1.2, and Table 14.2.2.1.3.

Effect of ADA on PK

Analyses of the data considering ADA status of the participants were conducted in the PK equivalence study RI-01-003 in RA patients. The main population for PK analysis excluded ADA positive patients. PK Sensitivity Analysis 1 Population included all patients irrespective of ADA status (both ADA positive and negative) and forced randomization patients. PK Sensitivity Analysis 2 Population excluded patients with confirmed positive ADA and forced randomization patients.

Study results indicated that PK parameters in the main population were comparable to the two sensitivity populations. Their 91% CIs for the ratios of the geometric means for the primary and secondary PK endpoints met the pre-specified acceptance criteria (80.00% to 125.00%).

It can be concluded that PK parameters were comparable irrespective of ADA status. No differences between DRL_RI and the innovator products were detected.

2.6.2.2. Pharmacodynamics

Mechanism of action

The MoA of rituximab is well characterised: Rituximab binds to both malignant B-cells with CD-20 expression, as well as to normal B-cells. Rituximab is used in haemato-oncology indications to deplete circulating and tissue-based malignant B cells. It is also used in auto-immune disorders to deplete peripheral B cells responsible for the production of pathogenic autoantibodies, and other intercellular mediated downstream effects that result in auto-immune response.

Upon binding to CD20, rituximab mediates B cell depletion by three distinct modes of action: antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. The

known pharmacological effect of rituximab is a rapid depletion of peripheral B cells, followed by a slow recovery over months.

Primary pharmacology

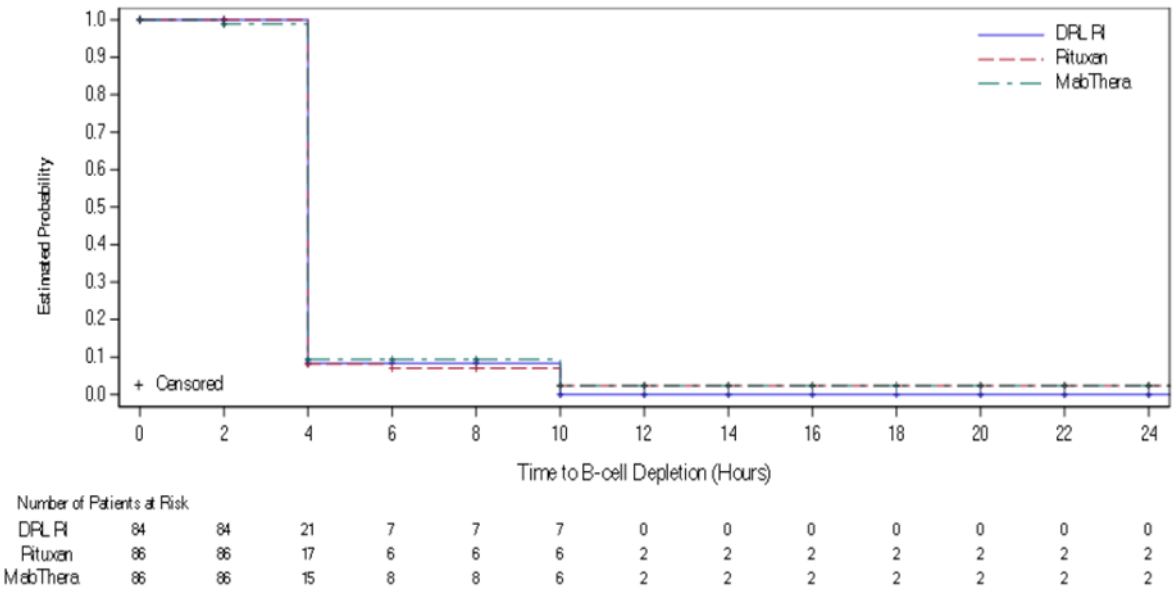
PD evaluation in terms of depletion and repletion of peripheral B-cells over time was part of secondary endpoints in study RI-01-003 and exploratory endpoints in study RI-01-006. Depletion of B cells occurs as a direct response to rituximab exposure and is rapid and complete following administration of rituximab. Repletion occurs more slowly over a period of 6 months, and B-cell repletion was monitored over 13 months in study RI-01-003 and 7 months in study RI-01-006 (long-term follow-up is ongoing). Though depletion and repletion of peripheral B-cells over time are not validated markers for assessment of efficacy, the data was collected and presented to ensure that the changes in these parameters follow the same pattern as that of change in efficacy.

Disease-activity score 28-C-reactive protein (DAS28-CRP) was monitored in study RI-01-003 up to Week 16 as a PD endpoint and at Week 24 as an efficacy endpoint. Thus, DAS28-CRP was considered as efficacy parameter so that improvement over time can be compared as requested by EMA and is therefore discussed in the Clinical efficacy Section.

PD results

In the PK equivalence study RI-01-003, B-cell depletion was rapid (median time to depletion of 3 hours) with the majority of patients depleted to levels below 20% of LLN within 10 hours after the first infusion. B-cell repletion started around Week 26, and repletion profiles appeared comparable across treatment arms up to Week 52.

Figure 6 Kaplan-Meier plot for time to B-cell depletion (below 20% of LLN - PD population)



Number of Patients at Risk

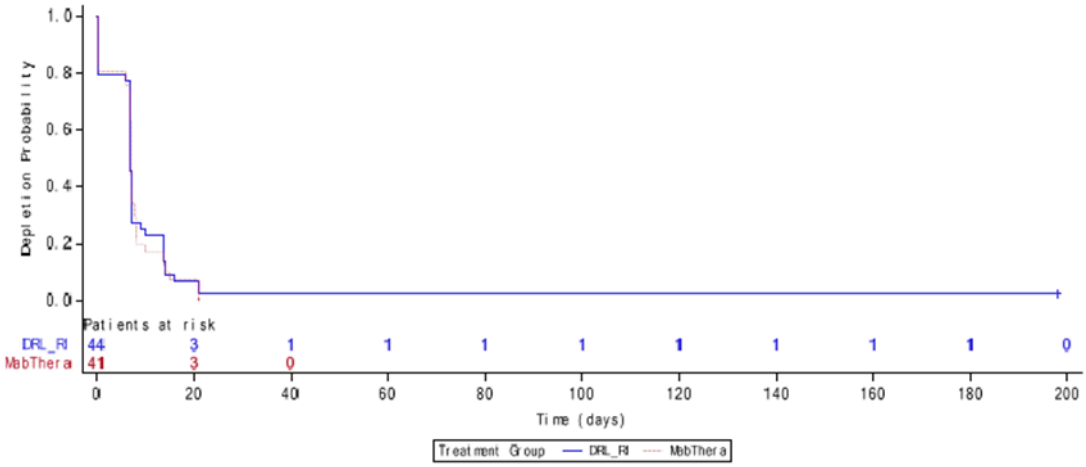
DRL RI	84	84	21	7	7	7	0	0	0	0	0	0	0
Rituxan	86	86	17	6	6	6	2	2	2	2	2	2	2
MabThera	86	86	15	8	8	6	2	2	2	2	2	2	2

The confidence intervals are estimated based on the Kaplan-Meier estimation method. The p-value is computed based on log-rank test.
Patients who did not experience depletion are censored.
*PD population for B cell are as evaluated in blinded data review meeting (Listing 16.2.3.2.4).
Patient 1001006, 1024002 and 2006006 are excluded from this analysis because already depleted at baseline

Though not surrogate biomarkers for efficacy, both B-cell depletion and repletion showed similar direction of change as expected, in line with the known mechanism of action of rituximab.

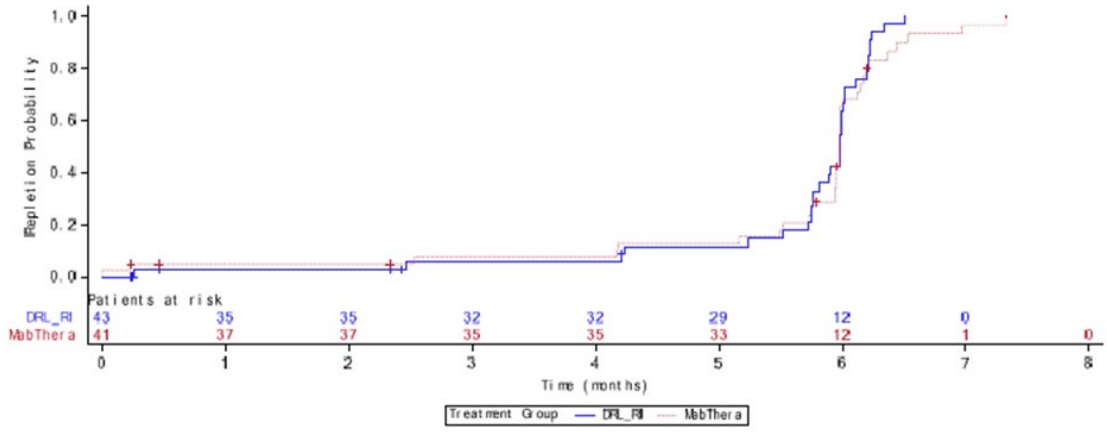
In the Phase 3 study RI-01-006, peripheral blood B-cell count data are presented as exploratory endpoints from the PD analysis set. Arithmetic mean rituximab plasma concentrations were overall comparable between the DRL_RI and MabThera arms at pre- and post-treatment time points. In both groups, most of the participants reached peripheral B-cell depletion below the lower limit of quantification (4 cells/µL) following completion of the first dose and remained below the limit of quantification up to Week 28.

Figure 7 Kaplan-Meier plot for time to B-cell depletion (PD Analysis set)



Abbreviations: DRL_RI = Dr Reddy's rituximab.
Time to B-cell depletion: Time from date of randomization to the first occurrence of a value below the lower limit of quantification; Subjects with a B-cell count below the lower limit of quantification at baseline were not included in this evaluation.

Figure 8 Kaplan-Meier plot for time to B-cell repletion (PD Analysis set)



Abbreviations: DRL_RI = Dr Reddy's rituximab.

In study RI-01-006, for the subjects that received DRL_RI for whom B-cell counts BLQ were not achieved, the B-cell counts were higher than in MabThera group. The Applicant was asked to analyze the possible reasons of such results including the issue of ADA presence. The data analysis revealed that, in both treatment arms, the majority of patients in the PD subset achieved B-cell depletion BLQ after a single dose of rituximab. Throughout the study, the distribution of patients with B-cell counts BLQ was similar between the treatment arms, with very few patients having counts above BLQ.

The Applicant asserts that the sample size of the pharmacodynamic subset population was relatively small, so slight imbalances can be expected due to inter-subject fluctuations. B-cell depletion is considered a more clinically meaningful parameter than the achievement of BLQ, and the B-cell depletion and repletion graph indicates a similar response between the treatment arms.

An analysis of subjects with B-cell counts >BLQ from Week 4 till EOS identified a single ADA-positive subject in the DRL_RI group at weeks 8 and 28, subsequently becoming negative at week 44 without impacting B-cell count at that time. Population PK and PD modelling analysis, pooling data from studies RI-01-003 and RI-01-006, confirmed no differences in the relationship between PK and B-cell count across different treatment arms. The final model effectively characterized B-cell count in both studies, supporting the conclusion that no differences were identified in the relationship between PK and B-cell count across treatment arms in the population PK and PD modelling analysis.

Table 7: Peripheral Blood B-cell Counts (PD Analysis Set)

Parameter	DRL_RI (N=44)			MabThera (N=41)		
	n_{BLQ}	n	Mean (SD), (cells/µL)	n_{BLQ}	n	Mean (SD), (cells/µL)
Prior to initiation of infusion at Week 1	1	43	466.6 (2032.41)	0	41	310.7 (682.25)
Prior to end of the infusion at Week 1	9	34	36.2 (87.79)	8	33	24.2 (30.84)
Prior to initiation of infusion at Week 2	33	8	6.3 (2.25)	34	5	10.2 (5.50)
Prior to initiation of infusion at Week 3	37	3	8.0 (4.58)	34	4	6.0 (2.71)
Prior to initiation of infusion at Week 4	38	5	16.2 (25.07)	36	1	8.0 (NC)
Prior to initiation of infusion at Week 12	35	4	37.5 (71.73)	35	1	6.0 (NC)
Prior to initiation of infusion at Week 20	35	3	170.0 (267.77)	35	1	5.0 (NC)
Prior to initiation of infusion at Week 28	36	2	171.5 (225.57)	31	3	5.7 (1.53)

Abbreviations: DRL_RI = Dr Reddy's rituximab; SD = standard deviation; BLQ = below the limit of quantification (4 cells/µL); N = number of subjects in the PD Analysis Set; n_{BLQ} = number of patients below BLQ; n = number of patients with available data.
Source: Study RI-01-006 Primary CSR-28 January 2023, Table 14.2.4.1 (Section 5.3.5.1.1)

In addition, in study RI-01-006 in the analysis of the AUEC of B-cell depletion between treatment arms, the GMR for the comparison DRL_RI/MabThera was 0.78 with 90%CI (0.47-1.32) and 95%CI (0.42-1.46). As the used equivalence margins for the assessment of PD were outside of the 80%-125% margins, the Applicant was asked to present the justification for the PD biosimilarity. In response, the Applicant stated that the AUEC of B-cell depletion in the study was exploratory and not designed or powered to meet equivalence criteria for PD parameters. This parameter was assessed in a subset of the population (90 patients).

In the RI-01-003 study, comparable proportions of patients achieved B-cell depletion when comparing DRL_RI to Rituxan and MabThera through Week 24. B-cell repletion profiles were also comparable across treatment arms up to Week 52. The Applicant also indicated that in the popPK/PD modelling using data from studies RI-01-003 and RI-01-006, no identified differences in the relationship between PK and B-cell count across different treatment arms were observed.

In summary, although the AUEC for B-cell counts was outside the typical value, it can be concluded that efficacy measures in clinical studies, together with the results of modelling, sufficiently support the PD equivalence between treatment arms.

Table 8: Linear Mixed Effects Comparison of the AUEC of B-cell Depletion Between Treatment Arms (PD Analysis Set)

	Difference: DRL_RI- MabThera			Ratio: DRL_RI/ MabThera		
	AM	90% CI	95% CI	GMR	90% CI	95% CI
AUEC (depletion) (cells/uL)*hours)	735598.58	(-1784223.16, 3255420.31)	(-2277493.48, 3748690.63)	0.78	(0.47, 1.32)	(0.42, 1.46)

Abbreviations: DRL_RI = Dr Reddy's rituximab; AUEC = area under the effect curve; AM = adjusted mean; CI = confidence interval; GMR = geometric mean ratio; PD = pharmacodynamic
Mixed model: Linear mixed-effects comparison of the AUEC of B-cell depletion is based on ANOVA models with treatment group as fixed effect. B-cells are defined as CD3-CD19+ cells determined by flow cytometry.
Source: Study RI-01-006 Primary CSR-28 January 2023, Table 14.2.4.3 (Section 5.3.5.1.1)

Rituximab Pharmacokinetics-Response Relationship Evaluation

The aims of this analysis were to describe the relationship of several efficacy parameters to rituximab plasma concentrations in patients with moderate to severe RA. Data for exposure-response analyses originate from study RI-01-003. The considered efficacy parameters were the changes in the RA disease activity score in 28 joints with DAS28-CRP and ACR 20, 50 and 70 improvement criteria. The final DAS28-CRP dropout model is a logistic regression model with an estimated base probability to dropout per month scaled by the time interval between two visits. The model included a relationship between the absolute, time-varying DAS28-CRP and dropout where higher DAS28-CRP predicted higher probability of dropout.

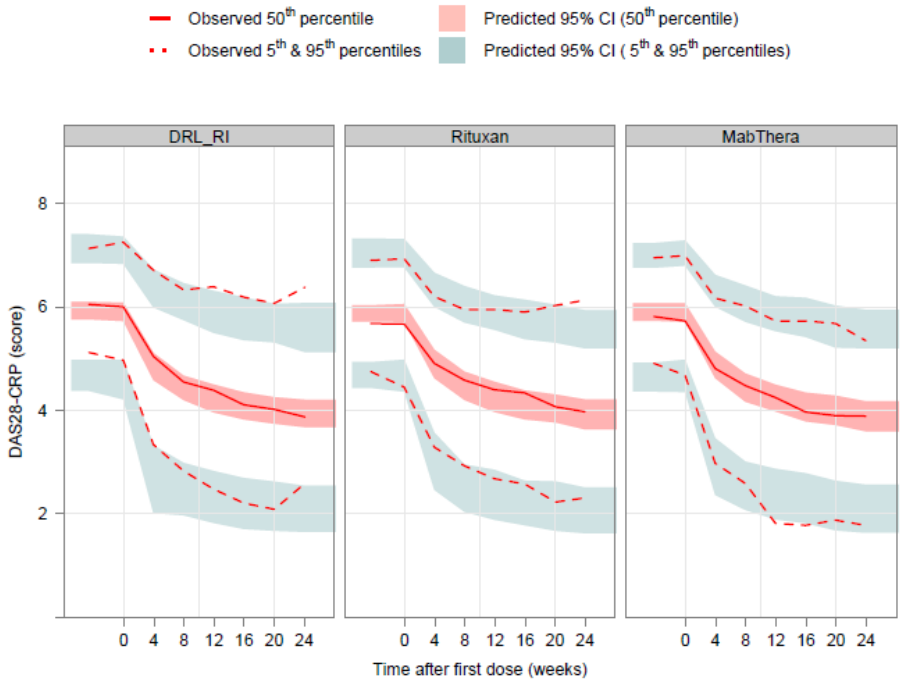
Table 9: Parameter estimates of the final DAS28-CRP model

	Final DAS28-CRP model
Run	3121
OFV	– 50.37
Condition number	107.15

		Final DAS28-CRP model		
	Unit	Value	RSE (%)	SHR (%)
$DAS28\text{-}CRP_{base}$ [a]		5.91	0.702	
K_{out} [a]	(/day)	0.00485	14.9	
TRT		0.723	6.62	
SLP [b]	ln(mL/µg)	-7.10	7.05	
HAQDIB on $DAS28\text{-}CRP_{base}$		0.255	12.7	
HAQDIB on K_{out}		0.570	23.8	
IIV $DAS28\text{-}CRP_{base}$	(SD)	0.262	5.50	11.1
IIV K_{out}	(CV)	1.04	6.98	16.9
IIV TRT	(CV)	0.634	8.09	25.5
IIV SLP	(CV)	1.25	30.1	30.2
Corr TRT-SLP		-0.923	17.8	
RUV additive	(SD)	0.416	1.23	14.4

[a] K_{in} was calculated as $DAS28\text{-}CRP_{base}$ multiplied by K_{out}.
[b] SLP was estimated on the exponential scale and corresponds to 8.27×10^{-4} mL/µg as a fractional increase in K_{out}
The RSE for IIV and RUV parameters are reported on the approximate SD scale.

Figure 9 VPC plot for absolute DAS28-CRP; median score and 90% PI predicted by final DAS28-CRP model.



The final ACR model is a discrete-time Markov model with five states: four ordered categorical states (ACR<20, ACR20-<50, ACR50-<70 and ACR70), in addition to a dropout state. The ACR categories were treated as exclusive (patients with ACR70 do not fulfil ACR50-<70 and ACR20-<50, patients with ACR50-<70 do not fulfil ACR20-<50) and not as cumulative categories.

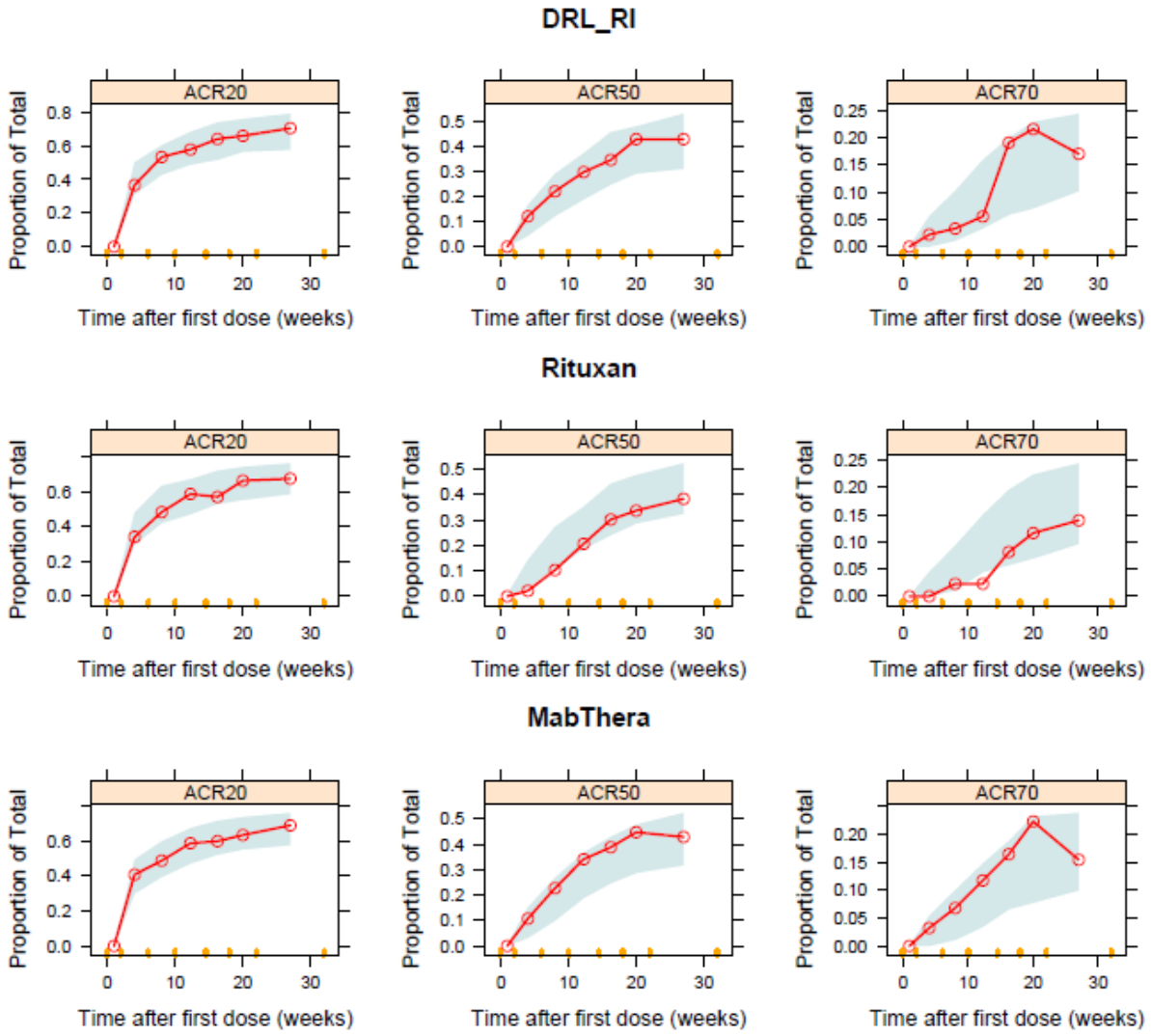
Table 10 Parameter estimates for the ACR model.

	Final model	Base model
Run	4063	4057
OFV	2936.75	2965.41
Condition number	63.94	51.74

		Final model		Base model	
	Unit	Value	RSE (%)	Value	RSE (%)
$LP_{ACR<20\rightarrow\geq ACR20}$	(logit)	-0.634	22.2	-0.638	23.1
$\theta_{ACR<20\rightarrow\geq ACR50}$	(logit)	-2.60	8.09	-2.60	8.02
$\theta_{ACR<20\rightarrow ACR70}$	(logit)	-1.94	16.4	-1.94	16.0
$LP_{ACR<20\rightarrow DO}$	(logit)	-3.85	6.19	-3.85	6.18
$LP_{ACR20\rightarrow\geq ACR20}$	(logit)	1.98	8.08	1.98	8.01
$\theta_{ACR20\rightarrow\geq ACR50}$	(logit)	-2.81	6.16	-2.81	6.06
$\theta_{ACR20\rightarrow ACR70}$	(logit)	-1.94	10.8	-1.94	10.3
$LP_{ACR50\rightarrow\geq ACR20}$	(logit)	2.77	10.2	2.77	9.99
$\theta_{ACR50\rightarrow\geq ACR50}$	(logit)	-1.32	18.0	-1.32	17.9
$\theta_{ACR50\rightarrow ACR70}$	(logit)	-2.54	7.74	-2.54	7.79
$LP_{ACR70\rightarrow\geq ACR20}$	(logit)	4.08	17.4	4.08	16.1
$\theta_{ACR70\rightarrow\geq ACR50}$	(logit)	-1.68	40.3	-1.68	36.1
$\theta_{ACR70\rightarrow ACR70}$	(logit)	-1.96	16.3	-1.96	16.5
$LP_{ACR20/50/70\rightarrow DO}$[a]	(logit)	-4.96	9.06	-4.96	9.05
HAQDIB on $LP_{ACR<20\rightarrow\geq ACR20}$[b]	(logit)	1.27	19.1		
IIV $LP_{ACR<20\rightarrow\geq ACR20}$	(SD)	1.53	11.5	1.68	11.3

[a]A single parameter was estimated to describe the probability of dropout for the ACR20-<50, ACR50-<70 and ACR70 categories. [b]Estimated as a linear relationship, on the logit scale. All parameters are reported on the logit scale and needs to be derived according to Section 4.3 to derive the corresponding probabilities. Derived probabilities are reported for the final model in the text section below.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.

Figure 10 VPC plots for the final ACR model - proportion of patients per cumulative category of ACR20, ACR50 and ACR70.



2.6.3. Discussion on clinical pharmacology

Clinical pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of DRL_RI, rituximab-EU, and rituximab-US were evaluated in a PK similarity study (study RI-01-003 in RA patients) and in a comparative efficacy, safety, PD, Pop PK and immunogenicity study (study RI-01-006 in LT-BFL patients). In an additional "single transition trial" (study RI-01-007 in RA patients), the impact of transition from Rituxan or MabThera treatment to DRL_RI was evaluated with regards to safety, immunogenicity, as well as time-matched rituximab concentrations (TMRC). In the pivotal comparative efficacy study, only rituximab-EU (MabThera) was used as comparator.

Bioanalytical methods applied during the clinical developments included an enzyme-linked immunosorbent assay (ELISA) for measuring the concentrations of rituximab in human plasma, an affinity capture elution (ACE) based immunoassay for the detection of anti-drug (rituximab) antibodies (ADA) in human plasma, a cell-based assay for the detection of neutralizing antibodies (NAb) in human plasma and a Flow Cytometry Assay to evaluate B cells depletion. Analytical methods were shown to be fit for purpose.

Pharmacokinetics

A population-PK model was developed using the data from studies RI-01-003 and RI-01-006 for comparing PK of DRL_RI with MabThera and Rituxan (RI-01-003) or with MabThera (RI-01-006). The final population PK model for rituximab was a 2-compartment model with first order elimination. Other mechanistic models (TMDD binding model, saturable Michaelis-Menten elimination model, refined empirical models) that were tested did not improve data fit and the difference in CL was thus modelled as a shift in CL (introduction of covariates) following the second dose and subsequent doses. It appears that this approach was necessary to remove deficiencies in the structural model with regards to the nonlinear behaviour of the drug. RUV for PK was described by an additive model on the log-scale including an IIV term on RUV. In the final population PK model, weight, sex, and baseline DAS28-CRP were included as significant covariates.

Overall, VPC and GOF plots for the final popPK model show acceptable agreement with the data.

Statistical methods

The PK similarity study RI-01-003 was a randomised, multicentre, double-blind, parallel 3-way equivalence study comparing DRL_RI to MabThera and Rituxan in combination with stabilised doses of non-biological disease-modifying antirheumatic drugs (DMARDs) in patients with active RA.

Patients were randomized to treatment via a stratified block randomization stratified by gender and region. Forced randomisation was implemented from 01 Jan 2015 to 25 Sept 2025 to allow randomisation of subjects in case not all three treatments were available on site. To keep the number lower than 5% in total, the mechanism was deactivated after that point. Thirteen (13) subjects were force randomized. In 10 out of 13 cases treatment kits for two arms were available for randomisation. Only in three cases only one arm was available for assignment. Subjects, sites and (blinded) sponsor team were to remain blinded to forced randomization assignments. Sensitivity analyses showed no relevant impact of this approach. Overall, while the lack of adequate supply at sites is considered problematic and should be avoided, the impact of the 13 force randomized subjects is considered negligible for the given procedure.

The sample size is considered acceptable and sample size calculations can be approximately reproduced. It is noted though that no clear strategy was described to handle multiplicity over the three primary PK endpoints and the three comparisons (DRL_RI/Rituxan, DRL_RI/MabThera, Rituxan/MabThera; in total 9 analyses). Post hoc, given the results, this is not a major issue but considered a planning fault.

A blinded sample size re-assessment (BSSR) was planned to update the estimate of the variability (CV). The method to adjust for the potential impact of the sample size re-assessment by adjusting the nominal significance level from 5% to 4.5% (i.e. using a 91% CI rather than a 90% CI) is endorsed. The BSSR showed that the CVs were lower than assumed a priori and hence no adjustment to the sample size was made.

Results

In the pivotal PK similarity study RI-01-003 in RA patients, DRL_RI, Rituxan and MabThera exhibited similar PK profiles with regards to the primary PK endpoints AUC0-14 days, first infusion, AUC0-inf, entire course, and AUC0-t, second infusion. For the PK similarity comparisons of DRL_RI to each of the reference products (rituximab-EU and rituximab-US), the 91% CIs for the test-to reference ratios of AUC0-14 days, AUC0-inf and AUC0-t were within the bioequivalence acceptance criteria of 80.00% to 125.00%, demonstrating PK similarity among rituximab-US, rituximab-EU, and DRL_RI.

Also, all other exposure parameters such as Cmax first infusion, Cmax second infusion, and AUC0-t, entire course showed biosimilarity (90% confidence intervals contained within 80.00% to 125.00%).

The other PK parameters, including Cl, Vd, and T1/2 seemed in general similar between treatment. Nevertheless, there is uncertainty regarding the Vd. The observed range of Vd for DRL_RI (3.36-19.2 L) is higher than for MabThera (2.41-10.9 L) and higher than reported in the SmPC for MabThera (range 1.7 – 7.51 L). The Applicant provided an additional analysis of the data on Vd. It was revealed that in the case of individual subjects who took DRL_RI, unexpectedly high Vd was observed. Following the reanalysis of the data, excluding this subject, the Vd appears to be comparable between treatment arms. However, the Applicant did not present a rule that allows the identification of extreme results. There were no significant protocol deviations reported for the subject displaying this outlier. Baseline albumin, protein levels, liver enzymes, and serum creatinine values were within the normal reference range. Therefore, the probable reason for such a high Vd remains unclear. However, the phenomenon appears to be random.

Primary PK analyses was conducted in the pre-defined PK population including all evaluable patients with PK concentrations without significant protocol deviations and without any confirmed positive test result for ADA.

Sensitivity analyses for the primary endpoints were performed in two populations: in the PK population including ADA positive patients, and in the PK population excluding ADA positive and forced randomization patients. They were supportive for the primary analysis in the original PK population, since their 91% CIs for the ratios of GM met the acceptance criteria of 80.00 to 125.00%.

The obtained results indicated that DRL_RI is bioequivalent with reference drugs - MabThera and Rituxan.

The sparse drug concentration data from the Week 28 report for the Phase 3 study RI-01-006 in LTB-FL patients treated with either DRL_RI or MabThera indicate similar rituximab serum concentrations at each time point between the 2 treatment groups and support the conclusion that DRL_RI is biosimilar to MabThera also in this disease population.

No studies have been conducted on the PK profile of Ituxredi in special populations as well as studies that examined the interactions. However, for a biosimilar application such studies are not mandatory.

The popPK analysis demonstrated that PK of rituximab was adequately described using a two-compartment model with linear elimination from the central compartment. Sex was found as a covariate on CL- and V-related parameters, and was included in the final model as a scaling factor on body weight. The typical individual value of CL was estimated to be 8% lower after the second dose in study RI-01-003 and 28% lower after the second and subsequent doses in study RI-01-006, indicating a saturable elimination pathway due to target-mediated drug disposition.

As declared by the applicant, no differences in the PK of rituximab between drug products, as estimated by population PK modelling, were identified either in study RI-01-003 or in study RI-01-006.

In the single transition study RI-01-007 in RA patients, the study objective was to assess the immunogenicity and safety of transitioning subjects with RA from Rituxan/MabThera treatment to either DRL_RI treatment (“switch”) or to continued treatment with Rituxan/MabThera.

In this setting, time-matched serum rituximab concentrations (TMRC) were assessed at different time points, along with immunogenicity sampling. Those TMRC values were overall comparable between both treatment groups, DRL_RI and MabThera/Rituxan.

Pharmacodynamics

No separate PD studies were conducted for the Ituxredi.

PD evaluation in terms of depletion and repletion of peripheral B-cells over time was part of secondary endpoints in study RI-01-003 and exploratory endpoints in study RI-01-006.

DAS28-CRP was monitored in study RI-01-003 as efficacy parameter and is therefore discussed in more detail in the Clinical efficacy Section. A gradual reduction of the DAS28-CRP score was observed at Week 4, 8, 12 and 16. The magnitude of the reduction is comparable between all treatment arms.

Both in RA patients (with an in principle normal B-cell count at baseline) as well as in patients with LTB-FL (with increased B-cell count at baseline), DRL_RI significantly and rapidly reduced B-cell counts below the detection level. PD response of DRL_RI was overall similar to the comparator EU-rituximab.

In study RI-01-003 in RA patients, B-cell repletion started around Week 26, and repletion profiles appeared comparable across treatment arms up to Week 52.

In the Phase 3 study RI-01-006 in LTB-FL patients, most of the participants reached peripheral B-cell depletion below the lower limit of quantification (4 cells/µL) following completion of the first dose and remained below the limit of quantification up to Week 28.

Prior to initiation of the last infusion at Week 28, 36/44 subjects in the DRL_RI group and 31/41 subjects in the MabThera group reported B-cell counts below the lower limit of quantification. However, the number of subjects for whom the B-cell depletion was not achieved, starting form the week 4 is numerically higher in the DRL_RI group than MabThera. In addition, for the subjects that received DRL_RI for whom B-cell counts BLQ were not achieved, the B-cell counts were higher than in MabThera group. The Applicant was asked to analyse the possible reasons of such results including the issue of ADA presence. The data analysis revealed that, in both treatment arms, the majority of patients in the PD subset achieved B-cell depletion BLQ after a single dose of rituximab. Throughout the study, the distribution of patients with B-cell counts BLQ was similar between the treatment arms, with very few patients having counts above BLQ. The Applicant asserts that the sample size of the pharmacodynamic subset population was relatively small, so slight imbalances can be expected due to inter-subject fluctuations. B-cell depletion is considered a more clinically meaningful parameter than the achievement of BLQ, and the B-cell depletion and repletion graph indicates a similar response between the treatment arms. An analysis of subjects with B-cell counts >BLQ from Week 4 till EOS identified a single ADA-positive subject in the DRL_RI group at weeks 8 and 28, subsequently becoming negative at week 44 without impacting B-cell count at that time. Population PK and PD modelling analysis, pooling data from studies RI-01-003 and RI-01-006, confirmed no differences in the relationship between PK and B-cell count across different treatment arms. The final model effectively characterized B-cell count in both studies, supporting the conclusion that no differences were identified in the relationship between PK and B-cell count across treatment arms in the population PK and PD modelling analysis.

In the analysis of the AUEC of B-cell depletion between treatment arms, the GMR for the comparison DRL_RI/MabThera was 0.78 with 90%CI (0.47-1.32) and 95%CI (0.42-1.46). As the used equivalence margins for assessment of PD were outside of the typical 80-125, the as part of the justification for the PD biosimilarity, stated that the AUEC of B-cell depletion in the study was exploratory and not designed or powered to meet equivalence criteria for PD parameters. This parameter was assessed in a subset of the population (90 patients).

In the RI-01-003 study, comparable proportions of patients achieved B-cell depletion when comparing DRL_RI to Rituxan and MabThera through Week 24. B-cell repletion profiles were also comparable across treatment arms up to Week 52. It was also indicated that in the popPK/PD modelling using data from studies RI-01-003 and RI-01-006, no identified differences in the relationship between PK and B-cell count across different treatment arms were observed. In summary, although the AUEC for B-cell counts was outside the typical value, it seems that efficacy measures in clinical studies, together with the results of modelling, sufficiently support the PD equivalence between treatment arms.

Rituximab is known to effectively reduce the peripheral CD19+ B–cell counts. However, there is no strong correlation between the extent of peripheral B-cell reduction and clinical response in RA, as RA disease activity may still remain even at low B-cell counts. For lymphoma, the correlation is neither clear, since circulating B-cells may not directly reflect tumour mass, and CD19+ cell counts alone cannot be considered as a surrogate of the clinical response.

Though not surrogate biomarkers for efficacy, both B-cell depletion and repletion showed similar direction of change as expected, in line with the known mechanism of action of rituximab.

A DAS28-CRP model and an ACR model were developed with the aim of describing PKPD characteristics of multiple PD and efficacy endpoints for rituximab with special focus on assessing the impact of differences between DRL_RI, MabThera and Rituxan. According to the VPC plots provided, the data simulated by both models described the observed data overall well. A clinically meaningful effect of treatment arm was not identified in any of the final exposure-response models (DAS28-CRP and ACR model).

2.6.4. Conclusions on clinical pharmacology

Generally, the PK/PD clinical programme seems adequate. Overall, the submitted data are considered supportive for demonstration of biosimilarity.

2.6.5. Clinical efficacy

The clinical development program for DRL_RI comprises three studies.

Study RI-01-006, a randomised, double-blind, parallel-group, Phase 3 study to compare the efficacy, safety, and immunogenicity of DRL_RI with MabThera in patients with previously untreated, stage II-IV LTB-FL, is considered the pivotal trial for demonstrating equivalence in efficacy.

In addition, **Study RI-01-003**, a randomised, double-blind, parallel 3-way equivalence study comparing DRL_RI to MabThera and Rituxan was performed with the primary objective to demonstrate equivalence in PK and pharmacodynamics at Week 24 in patients with active RA.

The objective of the third study, **RI-01-007**, a single transition supportive Phase 3 study in RA patients, was to assess the immunogenicity and safety after switching from Rituxan or MabThera to DRL_RI. Pharmacodynamics and efficacy were not evaluated in this study.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Pivotal efficacy study									

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
RI-01-006	142 sites, 17 countries	DB, R, P	DRL_RI or MabThera i.v. 375 mg/m2 Induction: q4w Maintenance: q8w Up to week 36	Equivalence of Efficacy and Safety	N=317 DRL_RI: 162 MabThera:155	57 weeks Screening: 5 Treatment: 36 FU: 16	M 157 F 160 Median Age 58.0	Stage II-IV, CD20-positive, LTB-FL	BORR up to week 28
Supportive studies									
RI-01-003	29 sites, 2 countries (India and Ukraine)	DB, R, P	DRL_RI, Rituxan, or MabThera 1000 mg i.v., Days 1, 15	Equivalence of PK/PD	N=276 DRL_RI: 91, Rituxan: 92, MabThera: 93	58 weeks Part 1: screening: 6, Treatment: 24 Part 2 (FU): 28	M 33 F 243 Median Age 46.0	Moderate to severe active, seropositive RA	$AUC_{0\text{-}14\ days}$ (first infusion) $AUC_{0\text{-}\infty}$ (entire course) $AUC_{0\text{-}t}$ (second infusion)
RI-01-007	46 sites, 7 countries	DB, R, P	DRL_RI or Rituxan/MabThera 1000 mg i.v., Days 1, 15	Safety, immunogenicity	N=140 DRL_RI: 70 Rituxan or MabThera: 70	28 weeks Screening: 2 weeks Treatment: 2 FU: 24	M 25 F 115 Median Age 62.0	Active RA	Incidence of - ADA and Nab - TEAE, SAE - anaphylactic reactions, hypersensitivity - IRRs

2.6.5.1. Dose-response studies

Not applicable.

2.6.5.2. Main study

Study 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 Tumour Burden Follicular Lymphoma*

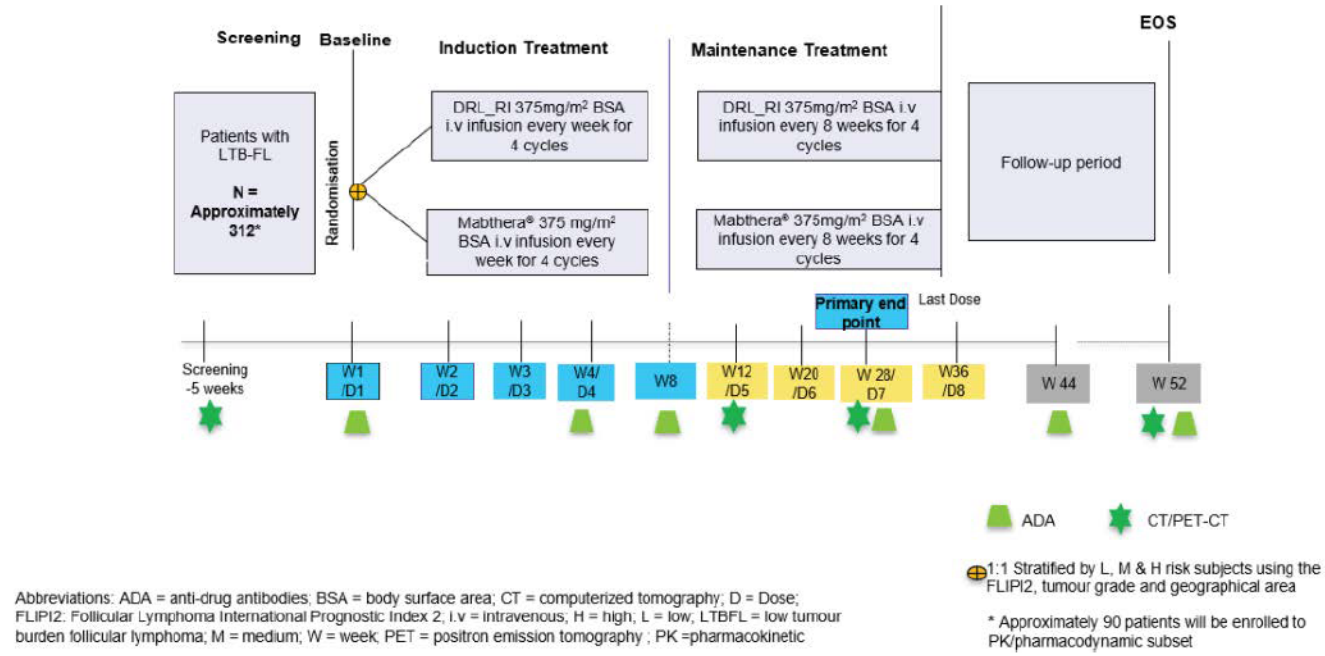
Methods

Study RI-01-006 is a randomised, double-blind, parallel-group, Phase 3 study to compare the efficacy, safety, and immunogenicity of DRL_RI with MabThera in patients with previously untreated, stage II-IV, CD-20 positive, LTB-FL. Eligible subjects were randomized in a 1:1 ration to receive either DRL_RI or EU approved MabThera.

Randomization was stratified by low-, medium-, and high-risk subjects using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2), as well as by tumour grade (1-2 Vs. 3a) and geographical area (United States of America [USA], Europe and Asia Pacific region).

Subjects received induction treatment with i.v. rituximab weekly for four cycles followed by maintenance treatment of i.v. rituxumab every 8 weeks starting at Week 12 until Week 36. After completion of the Maintenance Treatment Period, subjects were followed up till 52 weeks after the first dose of study drug (at Weeks 44 and 52).

Figure 11 - Study design of Study RI-01_006



Abbreviations: ADA = anti-drug antibodies; BSA = body surface area; CT = computerized tomography; D = Dose; FLIPI2: Follicular Lymphoma International Prognostic Index 2; I.v = intravenous; H = high; L = low; LTBFL = low tumour burden follicular lymphoma; M = medium; W = week; PET = positron emission tomography ; PK =pharmacokinetic

Study Participants

Male or female subjects aged ≥18 years with histologically confirmed Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per Groupe d'Etude des Lymphomes Folliculaires (GELF) based criteria. Subjects had Ann Arbor Stage II to IV and ECOG status of 0 to 1. Subject had at least 1 measurable tumour mass in 2 dimensions, and the mass was nodal lesion >15 mm in the longest dimension; or nodal lesion >10 mm to ≤15 mm in the longest dimension; and >10 mm in the shortest dimension; or extra-nodal lesion with both long and short dimensions ≥10 mm.

Patients with evidence of histologic transformation to high grade lymphoma or DLBC were excluded.

Patients had low tumour burden FL defined as: a) nodal or extranodal mass involvement with diameter measuring <7 cm, b) involvement of ≤3 nodal sites with diameter measuring >3 cm, c) Absence of systemic symptoms or B-symptoms (weight loss >10% within last 6 months, night sweats, fever >38°C for at least 3 days), d) Absence of splenomegaly, e) Absence of risk of vital organ compression, f) Absence of leukemic phase (count >5,000/µL of circulating tumour cells), g) Absence of clinically significant cytopenia (platelet count of <100,000/µL, haemoglobin <10 g/dL, or absolute neutrophil count <1,500/µL), h) Absence of clinically significant serous effusion based on clinical examination and CT scan, i) Serum LDH not higher than ULN.

Treatments

The study drug DRL_RI or MabThera was administered as an i.v. infusion, at a dose of 375 mg/m2 of BSA. Subjects received induction treatment consisting of 4 weeks (Day 1, 8, 15, 22) i.v. infusions followed by maintenance treatment consisting of an i.v. infusion every 8 weeks up to Week 36 (weeks 12, 20, 28 and 36). After completion of the Maintenance Treatment Period, subjects were followed up till 52 weeks after the first dose of study drug (at Weeks 44 and 52).

Study drug was administered by i.v. infusion using the escalating infusion rate in accordance with the EMA approved labelling for MabThera.

Subjects were pre-medicated before each infusion with an anti-pyretic and an antihistamine (e.g., paracetamol [acetaminophen] and diphenhydramine), and 100 mg i.v. methylprednisolone or their equivalent to decrease the incidence and severity of acute IRRs.

Objectives

The primary objective of this study was 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 (Cheson 1999).

The hypothesis was that the efficacy (as measured by best overall response rate [BORR] up to Week 28) of DRL_RI is equivalent to that of MabThera.

Secondary objectives were:

• To compare the ORR at Week 12 and Week 28, CR at Week 28, CR as a best response up to Week 28, DOR, PFS and OS of DRL_RI with MabThera in subjects with CD20-positive, LTB-FL.

• To compare the safety, tolerability, and immunogenicity of DRL_RI with MabThera in subjects with CD20-positive, LTB-FL.

Exploratory objectives were:

- To compare ORR evaluated in accordance with the Lugano criteria in subjects with CD20-positive, LTB-FL treated with either DRL_RI or MabThera.

• To explore the PK parameters of DRL_RI and MabThera, using a population-PK modelling approach.

• To explore the pharmacodynamic parameters of DRL_RI and MabThera.

Outcomes/endpoints

Primary efficacy outcome

Best overall response rate (BORR), defined as the proportion of subjects in each treatment group that achieve a best overall response (BOR) of either complete response (CR), unconfirmed complete response (CRu), or partial response (PR) up to Month 7 (Week 28) based on central radiology review in accordance with the International Working Group (IWG) response criteria for malignant lymphoma (Cheson 1999).

Secondary efficacy outcome

• Overall response rate (ORR) at Week 12 and Week 28 based on central radiology review in accordance with published response criteria for malignant lymphoma.

• Complete response (CR) rate at Month 7 (Week 28).

• Complete response (CR) rate as a best response up to Month 7 (Week 28).

• Duration of Response (DOR) defined as ORR based on the Lugano criteria for those subjects with available positron emission tomography (PET) data the time from date of the first documentation of tumour response (CR, CRu or PR) to the date of first documentation of progressive disease (PD) or to death due to any cause up to 52 weeks/EOS

• Progression-free survival (PFS) defined as the time from date of randomization to the date of documented PD or death due to any cause.

• Overall survival (OS) defined as the time from date of randomization to the date of death from any cause up to 52 weeks/ EOS.

• Adverse events, clinical laboratory values, vital signs, and electrocardiogram (ECG).

• Anti-rituximab antibodies and their relationship with other outcome measures.

Exploratory efficacy outcome

• Overall response rate (ORR) based on the Lugano criteria for those subjects with available positron emission tomography (PET) data.

• Pharmacokinetic (PK) parameters (e.g., clearance and volume of distribution) for DRL_RI and MabThera were derived using a population-PK modelling approach.

• Potential differences in pharmacodynamic parameters (e.g., area under the effect curve [AUEC] of circulating B-cells depletion) for DRL_RI and MabThera were investigated.

Sample size

A sample size of 120 subjects per treatment group (240 total) was computed to give approximately 82% probability of demonstrating equivalence of test-to-reference assuming:

- The primary end point is ORR at week 28, with an expected response rate of 88.0%
- The true difference in proportions is -0.03 (3%)
- The equivalence margin is ±0.16 (-16%/16%)
- A type I error rate of 5% (one-sided test with alpha level of 2.5%)
- A 1:1 randomisation ratio

Allowing for up to 15% losses due to follow-up (dropout), up to 284 subjects (142 per group) were to be randomised to get 240 evaluable subjects.

Published data for rituximab versus watch and wait (Ardeshna et al, 2014; Lancet Oncol.) revealed a treatment effect of 82.2%, [76.3%, 88.2%]). The lower bound of the 95% CI (76.3%) can be viewed as the expected minimum improvement. A margin of ±16% was chosen to preserve approximately 80% of the effect size.

With protocol version 4 (27 Oct 2021), the margin was revised to ± 17% in order to preserve approximately 78% of the treatment effect. At the same time the primary endpoint was changed from ORR at week 28 to BORR up to week 28. All other assumptions remained the same. This led to an updated sample size of 218 evaluable subjects (109 per group) and in total 250 subjects to be randomized (125 per group).

Together with the above updates, the results of the blinded sample size recalculation (based on the updated margin and updated endpoint which were not yet implemented via the protocol or SAP) were available and led to a final sample size of 304 (see below).

Blinded sample size re-assessment

Due to uncertainty in BOR until Week 28 probability for MabThera, a blinded sample-size re-assessment (BSSR) was planned after ~50% of the previously planned subjects. The specifications were as for the initial sample-size calculation with the exception of the estimate for BOR until week 28, which was to be estimated in a blinded fashion but keeping the assumed -0.03 difference in BOR probabilities. If the updated sample size is ≤ 250, then 250 is kept as sample size; If the update is [251;400] this sample size is proposed to the Sponsor; If the sample size is > 400, a final sample size of 400 is recommended to the Sponsor. A BSSR plan was devised based on the updated assumptions and became effective on 01 Sept 2021.In the BSSR (dated 29 Sept 2021, data cut-off 29 June 2021) based on n = 147 subjects, the BOR was calculated as 76.2% based on central radiology review. The number of non-evaluable patients was 3 (2.0%). The sample size was hence re-estimated as 304 (152 per group).

Randomisation and blinding (masking)

A double-blind randomised controlled trial was used. Randomisation was to be stratified by low, medium, and high-risk subjects using FLIPI2, as well as by tumour grade (1-2 Vs. 3a) and geographical area (USA, Europe and Asia-Pacific region).

Per the BSSR plan a wide range of functions was granted access to the BSSR plan, results and outputs. These included the DMC members, different biostatistical functions and regulatory staff of the CRO tasked with the BSSR, and most notably the Clinical Development Head, Clinical Sciences Head, Group Lead Biostatistics and Staff responsible for Regulatory submission of the Applicant. The mentioned Applicant's personnel was to participate in the DMC meeting and hence had access to all BSSR results as presented to the DMC. While the Applicant claims that these functions were not involved in the study conduct, the seniority of the Applicant's personnel makes the adequate blinding of the trial at least questionable.

Statistical methods

Analysis sets

For efficacy analyses, two main analysis sets were defined, the ITT set (all randomised subjects) and the PPS (ITT set with ≥ 1 dose of treatment, measurable disease at BL, ≥ 1 valid response evaluations and no major protocol deviations). Prohibited treatment was considered as non-responder in the PPS if given after PD. Both, ITT and PPS were considered as primary analysis sets.

Additional analysis sets were defined for specific purposes: the safety set, the PK analysis set, and the PD analysis set.

Primary analysis and sensitivity analyses

Two-sided 90% and 95% CIs for the difference in BOR up to Week 28 probability difference (DRL_RI minus MabThera) were obtained by the unstratified exact score method (Chan 1999). For FDA, biosimilarity was concluded (i.e., the null hypothesis rejected) if the 90% CI is completely contained within the predefined interval (-0.17, 0.17). For EMA, biosimilarity was concluded (i.e., the null hypothesis rejected) if the 95% CI is completely contained within the predefined interval (-0.17, 0.17). Equivalence was first assessed using the FDA criteria and then, if concluded, using the EMA criteria.

As sensitivity analysis, two-sided 90% and 95% CIs for the BOR up to Week 28 common probability difference between treatment groups (DRL_RI minus MabThera) was obtained using the stratified Mantel-Haenszel method, stratified by the strata used in the stratified randomization.

Further sensitivity analyses were defined in the protocol and SAP. Additionally, intercurrent events were defined in the SAP and an estimand and a sensitivity estimand were defined for the EMA and different ones for the FDA starting with SAP v3.0 (31 Jan 2022) and finalized in SAP v4.0 (18 Aug 2022). A description of the multiple imputation methods is provided in SAP v4.0.

Conduct of study / changes to key statistical aspects

As discussed above in the sample size section, the primary endpoint and corresponding assumptions were changed rather late in the trial. These changes were used for the blinded sample size re-assessment before being implemented via an SAP or protocol amendment.

Results

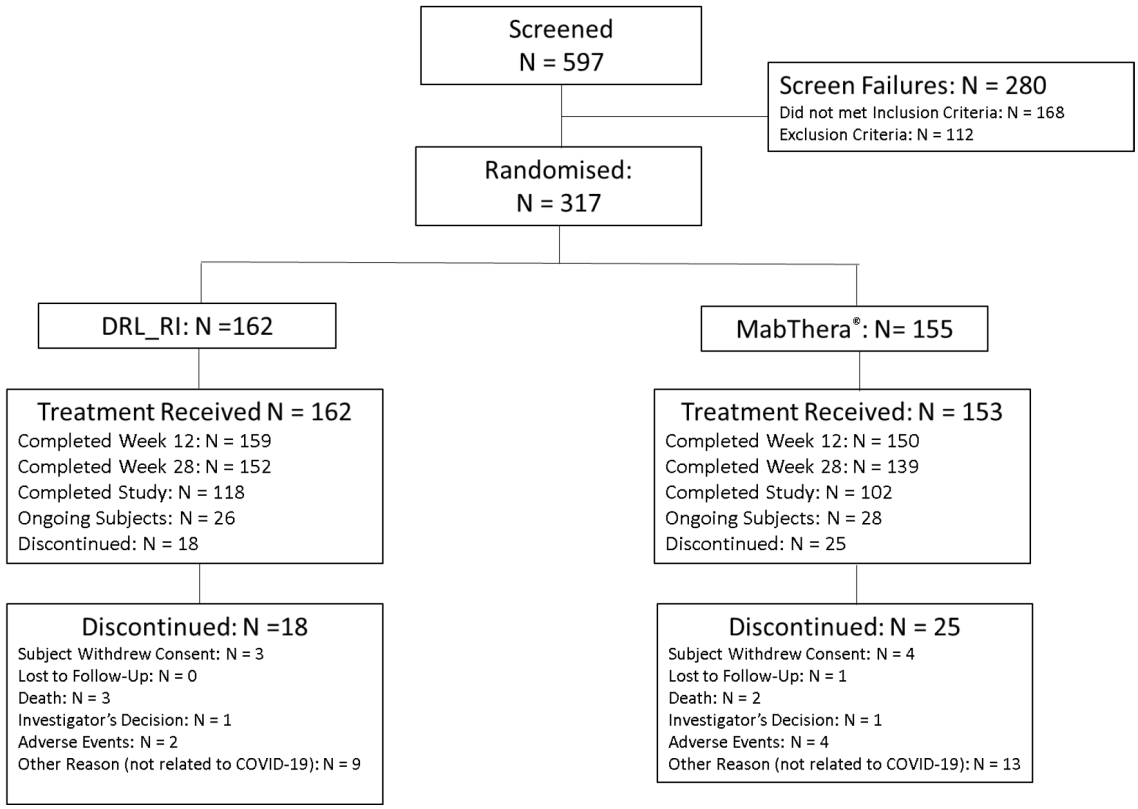
Participant flow

A total of 317 subjects were recruited and randomized to receive either DRL_RI or MabThera in the study; 162 subjects were assigned to the DRL_RI group and 155 subjects to the MabThera group. As of 21 Sep 2022:

• A total of 309 subjects (97.5%) completed Week 12 visit; 159 subjects (98.1%) in the DRL_RI group and 150 subjects (96.8%) in the MabThera group.

• A total of 291 subjects (91.8%) completed Week 28 visit; 152 subjects (93.8%) in the DRL_RI group and 139 subjects (89.7%) in the MabThera group.

• A total of 220 subjects (69.4%) have already completed the study (EOS visit); 118 subjects (72.8%) in the DRL_RI group and 102 subjects (65.8%) in the MabThera group.



Reasons for discontinuation

Of the 162 subjects receiving DRL_RI, a total of 18 subjects (11.1%) were discontinued during the study. Of the 18 subjects who discontinued from DRL_RI group, 3 subjects (1.9%) withdrew consent, 2 subjects (1.2%) discontinued due to AEs and 9 subjects (5.6%) discontinued due to other reasons (disease progression, except single subject). Three subjects (1.9%) died and 1 subject (0.6%) was withdrawn due to Investigator's decision. Of these 3 deaths, 2 subjects died while on treatment and one subject died posttreatment. Both the subjects who died on treatment were in the Maintenance Treatment Period; of which, one subject received 5 doses and other subject received 6 doses in this study.

Of the 153 subjects receiving MabThera, a total of 25 subjects (16.1%) were discontinued during the study. Of the 25 subjects who discontinued from MabThera group, 4 subjects (2.6%) withdrew consent, 1 subject (0.6%) subject lost to follow-up, 4 subjects (2.6%) discontinued due to AEs and 13 subjects (8.4%) discontinued due to other reasons (disease progression, except single subject). Two subject (1.3%) died and 1 subject (0.6%) was withdrawn due to Investigator's decision. Of these 2 deaths, both the subjects died posttreatment.

Recruitment

Date of First Subject Screened: 15 May 2019

Date of Last Subject Completed: 13 Sep 2022 (Week 28 visit)

Data cut-off date for submitted CSR: 21 Sep 2022

Date of CSR: 28 Jan 2023 (Week 28 Clinical Study Report)

Study Completion Date: The study was ongoing (in follow-up) at the time of submission. All study data up to and including the Week 28 study visit have been included in the CSR. In the specific case of subject disposition and DOR, all available data up to the cut-off date of 21 Sep 2022 are included. Another CSR will be generated with data up to Week 52 (study completion) which will provide full information about the study.

Conduct of the study

Protocol amendments

The original protocol was amended four times. The main changes are summarized below.

Protocol Amendment No. 1, dated 04 Jan 2019:

- Addition of exclusion criteria # 6: known Central Nervous system (CNS) involvement by lymphoma.
- Addition of text "especially the detailed algorithm for sample size re-estimation and simulations to show that the type-I error rate is maintained" based on protocol review-non-hold comments from US FDA.
- Changed from "The estimated difference (DRL_RI minus MabThera) and its 95% CI will be obtained using the stratified Miettinen and Nurminen method" to the estimated difference (DRL_RI minus MabThera) and its 95% CI will be obtained. The estimated difference (DRL_RI minus MabThera) and its 95% CI will be obtained using the test-based exact Binomial confidence interval method". Based on protocol review-non-hold comments from US FDA.

Protocol Amendment No. 2, dated 04 Dec 2019:

- Screening period changed from -4 weeks to -5 weeks, for administrative reasons considering longer turnaround time (TAT) of central histopathology lab evaluation report.
- tissue sample and bone marrow biopsies time changed from 6 months to 12 months and 6 weeks to 12 weeks, respectively. Added in the interest of subject, invasive nature of procedure and indolent course of disease under study.
- Complete Response (CR) rate at Month 7 (Week 28), added to comply with Regulatory Authority advice. Rearrangement of the secondary endpoints to follow the chronological order in which they were determined in the Study.
- Exclusion criteria regarding prior malignancies and subjects with tuberculosis (TB) were amended.
- Tumour grade and geographical area details specified "tumour grade (1-2 Vs. 3a), and geographical area (USA, Europe and Asia Pacific region)", for better clarity and to elaborate on the randomization strata.
- Text added, to reflect set up of DMC for the study.
- Updated parameters for screening tests (FSH, TB).

Protocol Amendment No. 3, dated 04 Nov 2020:

- Updated to allow for study inclusion of subjects with past history of hepatitis B or hepatitis B serology suggestive of past hepatitis B infection and subjects with history of hepatitis C while ensuring that the management practices for this condition are in line with current scientific guidelines. As a consequence, hepatitis testing was added.

- Anti-DRL_RI antibodies changed to Anti-rituximab antibodies to reflect the actual assessment and better clarity.
- COVID-19 information and details related HBV antiviral prophylaxis therapy added for consistency and clarity.
- Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF based criteria updated for clarity and consistency with rest of the protocol.
- Serum pregnancy test added for improved implementation and clarity.
- Included "On the basis of B-cell counts a population pharmacodynamics evaluation including population pharmacokinetics-pharmacodynamics evaluation might be performed which will be evaluated in a separate analysis plan" for clarity.

Protocol Amendment No. 4, dated 27 Oct 2021:

- Number of subjects to be randomized was updated to 312 from up to 284, based on the revision in the sample size calculation assumptions and blinded sample size re-estimation.
- Primary endpoint updated to "the primary endpoint is BORR, defined as the proportion of subjects in each treatment group that achieve a best overall response of either CR, CRu or PR up to Month 7 (Week 28) based on central radiology review in accordance with the response criteria for malignant lymphoma". Based on the discussion with US FDA.
- Added ORR at Week 28 and CR rate as a best response up to Month 7.
- Updated in the equivalence margin to (-17%, 17%), based on the changes made in the 9.2, Sample size determination.
- Included text regarding COVID-19 events based on the earlier changes belonged to addition of intercurrent events.

Protocol deviations

Protocol deviations were captured at individual visit specific requirements and at every parameter level based upon the routinely updated protocol deviation specification form. Therefore, the number of "Minor" deviations can be expected to be relatively higher. This approach was taken into the account to understand the deviations at granular level for every subject's specific requirement.

Table 11 Summary of Major and Minor Protocol Deviations (ITT Analysis Set)

Number (%) of Subjects	DRL_RI (N=162) n (%) E	MabThera® (N=155) n (%) E	Overall (N=317) n (%) E
With any protocol deviations [1]	156 (96.3) 1898	152 (98.1) 1629	308 (97.2) 3527
With at least one major protocol deviation	74 (45.7) 216	79 (51.0) 210	153 (48.3) 426
AE/SAE	1 (0.6) 1	2 (1.3) 2	3 (0.9) 3
Inc/excl criteria	3 (1.9) 3	3 (1.9) 4	6 (1.9) 7
Informed consent	1 (0.6) 1	3 (1.9) 3	4 (1.3) 4
IP admin/study treat	16 (9.9) 18	12 (7.7) 19	28 (8.8) 37
Procedures/tests	60 (37.0) 171	63 (40.6) 159	123 (38.8) 330
Visit schedule	16 (9.9) 21	16 (10.3) 23	32 (10.1) 44
Withdrawal criteria	1 (0.6) 1	0	1 (0.3) 1
With at least one minor protocol deviation	153 (94.4) 1682	150 (96.8) 1419	303 (95.6) 3101
Informed consent	0	2 (1.3) 2	2 (0.6) 2
IP admin/study treat	117 (72.2) 517	110 (71.0) 449	227 (71.6) 966
Other	19 (11.7) 19	24 (15.5) 27	43 (13.6) 46
Procedures/tests	138 (85.2) 1081	130 (83.9) 879	268 (84.5) 1960
Visit schedule	47 (29.0) 65	44 (28.4) 62	91 (28.7) 127

Source: Table 14.1.2.1

Abbreviation: AE = adverse event; ITT = Intent to Treat; E = number of events; excl = exclusion; inc = inclusion; IP = investigational product; SAE = serious adverse event

n: The number of subjects in specific category; N: The number of subjects in the ITT Analysis Set; nPD: The number of total protocol deviations in specific category.

[1] Includes subjects with COVID-19 related protocol deviations.

%: Calculated using the number of subjects in the ITT Analysis Set for each treatment group, or overall study group, as denominator (n/N*100).

All Protocol Deviations up to Week 28 only reported.

Table 12 - Summary of Protocol Deviations Due to COVID-19 Pandemic (ITT Analyses Set)

Number (%) of Subjects	DRL_RI (N=162) n (%) E	MabThera® (N=155) n (%) E	Overall (N=317) n (%) E
With any protocol deviations	10 (6.2) 13	10 (6.5) 17	20 (6.3) 30
With at least one major protocol deviation	3 (1.9) 3	6 (3.9) 8	9 (2.8) 11
AE / SAE	0	1 (0.6) 1	1 (0.3) 1
IP Admin/Study treatment	1 (0.6) 1	1 (0.6) 1	2 (0.6) 2
Procedures/Tests	1 (0.6) 1	0	1 (0.3) 1
Visit schedule	1 (0.6) 1	5 (3.2) 6	6 (1.9) 7
With at least one minor protocol deviation	8 (4.9) 10	5 (3.2) 9	13 (4.1) 19
IP administration/Study treatment	1 (0.6) 1	0	1 (0.3) 1
Procedures/Tests	1 (0.6) 2	2 (1.3) 5	3 (0.9) 7
Visit schedule	6 (3.7) 7	3 (1.9) 4	9 (2.8) 11

Source: Table 14.1.2.2

Abbreviations: COVID-19 = coronavirus disease of 2019; E = number of events; IP = investigational product; ITT = Intent to Treat

n: The number of subjects in specific category; N: The number of subjects in the ITT Analysis Set; nPD: The number of total protocol deviations in specific category.

%: Calculated using the number of subjects in the ITT Analysis Set for each treatment group, or overall study group, as denominator (n/N*100).

All Protocol Deviations up to Week 28 only reported.

Information in the form of a "Note to file" on missing data from Ukrainian and Russian sites due to the Russia-Ukraine geopolitical conflict was provided. Data related to the primary endpoint was collected prior to the conflict.

Baseline data

Table 13 - Demographic Characteristics (ITT Analysis Set)

Characteristics	DRL_RI (N=162)	MabThera® (N=155)	Overall (N=317)
Age (years)			
N	162	155	317
Mean	57.6	55.8	56.7
StD	12.37	13.03	12.70
Median	58.0	57.0	58.0
Min, max	27, 87	22, 82	22, 87
Race			
White	104 (64.2)	107 (69.0)	211 (66.6)
Asian	51 (31.5)	46 (29.7)	97 (30.6)
Black or African American	0	0	0
American Indian or Alaska Native	0	0	0
Aboriginal/Torres Strait Islander	1 (0.6)	0	1 (0.3)
Native Hawaiians or Other Pacific Islanders	0	0	0
Unknown	1 (0.6)	1 (0.6)	2 (0.6)
Not Reported	5 (3.1)	1 (0.6)	6 (1.9)
Other	0	0	0
BSA (m^2)*			
n	162	154	316
Mean	1.848	1.855	1.851
StD	0.2462	0.2513	0.2483
Median	1.825	1.850	1.835
Min, max	1.21, 2.69	1.19, 2.82	1.19, 2.82
Age group			
< 60yrs	89 (54.9)	90 (58.1)	179 (56.5)
≥ 60yrs	73 (45.1)	65 (41.9)	138 (43.5)
Gender			
Female	82 (50.6)	78 (50.3)	160 (50.5)
Male	80 (49.4)	77 (49.7)	157 (49.5)
Height (cm)			
n	162	155	317
Mean	166.79	166.97	166.87
StD	10.291	9.819	10.047
Median	165.00	167.00	166.10
Min, max	146.0, 196.0	141.0, 197.0	141.0, 197.0

Weight (kg)			
n	162	155	317
Mean	75.21	75.89	75.54
StD	17.735	18.346	18.011
Median	72.20	74.20	73.00
Min, max	35.0, 163.0	36.0, 153.0	35.0, 163.0
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	44 (27.2)	45 (29.0)	89 (28.1)
White	63 (38.9)	61 (39.4)	124 (39.1)
Black	0	0	0
Asian	51 (31.5)	46 (29.7)	97 (30.6)
Multiracial	0	0	0
Native	0	0	0
Not Reported	3 (1.9)	1 (0.6)	4 (1.3)
Unknown	1 (0.6)	2 (1.3)	3 (0.9)
Other	0	0	0
Geographical Region			
Asia Pacific	51 (31.5)	46 (29.7)	97 (30.6)
EU region	111 (68.5)	108 (69.7)	219 (69.1)
United States	0	1 (0.6)	1 (0.3)

Source: Table 14.1.4.1

Abbreviations: BMI = body mass index; BSA=body surface area; EU = European Union; ITT = Intention-to-Treat; max = maximum; min = minimum; StD = standard deviation.

n: The number of subjects in specific category; N: The number of subjects in the ITT Analysis Set.

Table 14 - Summary of Age Group (Years) Categories (ITT Analysis Set)

Age Group (Years)	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
<65	113 (69.8)	105 (67.7)	218 (68.8)
65-74	42 (25.9)	39 (25.2)	81 (25.6)
75-84	6 (3.7)	11 (7.1)	17 (5.4)
>=85	1 (0.6)	0	1 (0.3)

Source: Listing 16.2.4.1 and 16.2.4.2.1
ITT = Intent to Treat
n: The number of subjects in specific category; N: The number of subjects in the ITT Analysis Set.
%: Calculated using the number of subjects in the ITT Analysis Set for each treatment group, or overall study group, as denominator (n/N*100).

Table 15 - Summary of Age Grous (Years) Categories (PP Analysis Set)

Age Group (Years)	DRL_RI (N=158) n (%)	MabThera® (N=149) n (%)	Overall (N=307) n (%)
<65	109 (69.0)	103 (69.1)	212 (69.1)
65-74	42 (26.6)	37 (24.8)	79 (25.7)
75-84	6 (3.8)	9 (6.0)	15 (4.9)
>=85	1 (0.6)	0	1 (0.3)

Source: Listing 16.2.4.1 and 16.2.4.2.1
PP = Per Protocol
n: The number of subjects in specific category; N: The number of subjects in the PP Analysis Set.
%: Calculated using the number of subjects in the PP Analysis Set for each treatment group, or overall study group, as denominator (n/N*100).

Table 16- Summary of Demographic Characteristics (Subjects with Grade 2 Tumor Grade) (ITT Analysis Set) - Excerpt

Characteristics	DRL_RI (N=37)	MabThera® (N=33)	Overall (N=70)
Age (years)			
n (%)	37	33	70
Mean	55.1	54.9	55.0
SD	11.72	14.14	12.82
Median	57.0	59.0	57.0
Min, max	32, 83	22, 78	22, 83
Age group			
< 60yrs	24 (64.9)	19 (57.6)	43 (61.4)
>= 60yrs	13 (35.1)	14 (42.4)	27 (38.6)
Gender			
Male	21 (56.8)	16 (48.5)	37 (52.9)
Female	16 (43.2)	17 (51.5)	33 (47.1)
Geographical Region			
Asia Pacific	7 (18.9)	8 (24.2)	15 (21.4)
EU region	30 (81.1)	25 (75.8)	55 (78.6)

Table 17 - Summary of Demographic Characteristics (Subjects with Grade 3a Tumor Grade) (ITT Analysis Set) - Excerpt

Characteristics	DRL_RI (N=24)	MabThera® (N=26)	Overall (N=50)
Age (years)			
n (%)	24	26	50
Mean	61.7	54.6	58.0
SD	12.21	12.81	12.90
Median	64.0	55.0	60.0
Min, max	34, 83	27, 76	27, 83
Age group			
< 60yrs	9 (37.5)	16 (61.5)	25 (50.0)
>= 60yrs	15 (62.5)	10 (38.5)	25 (50.0)
Gender			
Female	14 (58.3)	14 (53.8)	28 (56.0)
Male	10 (41.7)	12 (46.2)	22 (44.0)
Geographical Region			
Asia Pacific	4 (16.7)	5 (19.2)	9 (18.0)
EU region	20 (83.3)	20 (76.9)	40 (80.0)
United States	0	1 (3.8)	1 (2.0)

Table 18 - Baseline Characteristics (ITT Analysis Set)

Characteristics	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
ECOG Performance Status			
0	128 (79.0)	122 (78.7)	250 (78.9)
1	34 (21.0)	31 (20.0)	65 (20.5)
≥ 2	0	0	0
Missing	0	2$ (1.3)	2 (0.6)
Serum beta-2 microglobulin			
Normal	129 (79.6)	126 (81.3)	255 (80.4)
Raised above upper limit of normal	33 (20.4)	29 (18.7)	62 (19.6)
Hemoglobin level			
< 120 g/L	15 (9.3)	22 (14.2)	37 (11.7)
≥ 120 g/L	147 (90.7)	133 (85.8)	280 (88.3)
Bone marrow involvement			
Absent	123 (75.9)	106 (68.4)	229 (72.2)
Present	39 (24.1)	49 (31.6)	88 (27.8)
Longest diameter of largest involved node for FLIPI2 score			
< 6 cm	155 (95.7)	146 (94.2)	301 (95.0)
≥ 6 cm	7 (4.3)	9 (5.8)	16 (5.0)
Overall FLIPI2 Score (eCRF)			
0	51 (31.5)	46 (29.7)	97 (30.6)
1-2	101 (62.3)	99 (63.9)	200 (63.1)
3-5	10 (6.2)	10 (6.5)	20 (6.3)
Overall FLIPI2 Risk Category (IWRS)			
Low Risk	60 (37.0)	56 (36.1)	116 (36.6)
Intermediate Risk	92 (56.8)	91 (58.7)	183 (57.7)
High Risk	10 (6.2)	8 (5.2)	18 (5.7)
Histological Tumor Grade for FL			
Grade 1	101 (62.3)	96 (61.9)	197 (62.1)
Grade 2	37 (22.8)	33 (21.3)	70 (22.1)
Grade 3a	24 (14.8)	26 (16.8)	50 (15.8)
Histological Tumor Grade for FL as per randomization strata			
Grade 1-2	138 (85.2)	129 (83.2)	267 (84.2)
Grade 3a	24 (14.8)	26 (16.8)	50 (15.8)

Source: Table 14.1.4.2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ITT = Intention-to-Treat; FLIPI2 = Follicular Lymphoma International Prognostic Index 2; FL = Follicular Lymphoma; IWRS = Interactive Web Response System.

n: The number of subjects in specific category; N: The number of subjects in the ITT Analysis Set.

%: Calculated using the number of subjects in the ITT Analysis Set for each treatment group, or overall study group, as denominator (n/N*100).

$ - These two subjects in MabThera® arm were randomized but not dosed hence, data was missing.

Table 19 - Summary of Baseline Characteristics (Subjects with Grade 2 Tumor Grade) (ITT Analysis Set) - Excerpt

Characteristics	DRL_RI (N=37) n (%)	MabThera® (N=33) n (%)	Overall (N=70) n (%)
ECOG performance Status			
0	30 (81.1)	26 (78.8)	56 (80.0)
1	7 (18.9)	7 (21.2)	14 (20.0)
>= 2	0	0	0
Serum beta-2 microglobulin			
Normal	27 (73.0)	27 (81.8)	54 (77.1)
Raised above upper limit of normal	10 (27.0)	6 (18.2)	16 (22.9)
Haemoglobin level			
< 120 g/L	2 (5.4)	5 (15.2)	7 (10.0)
>= 120 g/L	35 (94.6)	28 (84.8)	63 (90.0)
Bone marrow involvement			
Absent	26 (70.3)	26 (78.8)	52 (74.3)
Present	11 (29.7)	7 (21.2)	18 (25.7)
Overall FLIPI2 Risk Category (IWRS)			
Low Risk	17 (45.9)	12 (36.4)	29 (41.4)
Intermediate Risk	18 (48.6)	20 (60.6)	38 (54.3)
High Risk	2 (5.4)	1 (3.0)	3 (4.3)
Lactate Dehydrogenase (LDH) at Screening			
<=ULN	36 (97.3)	32 (97.0)	68 (97.1)
>ULN	1 (2.7)	1 (3.0)	2 (2.9)
Lactate Dehydrogenase (LDH) at Baseline			
<=ULN	34 (91.9)	30 (90.9)	64 (91.4)
>ULN	3 (8.1)	3 (9.1)	6 (8.6)

Table 20 - Summary of Baseline Characteristics (Subjects with Grade 3a Tumor Grade) (ITT Analysis Set) - Excerpt

Characteristics	DRL_RI (N=24) n (%)	MabThera® (N=26) n (%)	Overall (N=50) n (%)
ECOG performance Status			
0	16 (66.7)	19 (73.1)	35 (70.0)
1	8 (33.3)	6 (23.1)	14 (28.0)
>= 2	0	0	0
Missing	0	1 (3.8)	1 (2.0)
Serum beta-2 microglobulin			
Normal	18 (75.0)	19 (73.1)	37 (74.0)
Raised above upper limit of normal	6 (25.0)	7 (26.9)	13 (26.0)
Haemoglobin level			
< 120 g/L	2 (8.3)	4 (15.4)	6 (12.0)
>= 120 g/L	22 (91.7)	22 (84.6)	44 (88.0)
Bone marrow involvement			
Absent	21 (87.5)	19 (73.1)	40 (80.0)
Present	3 (12.5)	7 (26.9)	10 (20.0)
Longest diameter of largest involved node for FLIPI2 score			
< 6 cm	23 (95.8)	22 (84.6)	45 (90.0)
>= 6 cm	1 (4.2)	4 (15.4)	5 (10.0)
Overall FLIPI2 Risk Category (IWRS)			
Low Risk	10 (41.7)	9 (34.6)	19 (38.0)
Intermediate Risk	12 (50.0)	16 (61.5)	28 (56.0)
High Risk	2 (8.3)	1 (3.8)	3 (6.0)
Lactate Dehydrogenase (LDH) at Screening			
<=ULN	22 (91.7)	25 (96.2)	47 (94.0)
>ULN	2 (8.3)	1 (3.8)	3 (6.0)
Lactate Dehydrogenase (LDH) at Baseline			
<=ULN	22 (91.7)	21 (80.8)	43 (86.0)
>ULN	2 (8.3)	4 (15.4)	6 (12.0)
Missing	0	1 (3.8)	1 (2.0)

Numbers analysed

The ITT Analysis Set included all randomized subjects. The primary efficacy analysis was based on the ITT Analysis Set.

The sensitivity analysis was performed for the PP Analysis Set. The Per-Protocol Analysis Set (PPS) included all randomized subjects who received at least one dose of study drug, had measurable disease at Baseline as confirmed by central review, had an at least one available valid response evaluation up to Week 28 (± 4 weeks), had no major protocol deviations that would significantly impact the primary efficacy endpoint.

Table 21 - Summary of Analysis Sets

Number (%) of Subjects	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Total (N=317) n (%)
Intent to Treat Analysis Set	162 (100.0)	155 (100.0)	317 (100.0)
Per Protocol Analysis Set	158 (97.5)	149 (96.1)	307 (96.8)
Safety Analysis Set	162 (100.0)	153 (98.7)	315 (99.4)
Pharmacokinetic Analysis Set (planned is 90)	48 (29.6)	41 (26.5)	89 (28.1)
Pharmacodynamic Analysis Set (planned is 90)	44 (27.2)	41 (26.5)	85 (26.8)
Immunogenicity Analysis Set	160 (98.8)	152 (98.1)	312 (98.4)
eCRF FLIPI2 Risk Category Analysis Set[$]	162 (100.0)	153 (98.7)	315 (99.4)
eCRF Tumor Grade Analysis Set[$]	162 (100.0)	153 (98.7)	315 (99.4)

Source Table 14.1.3.1, Appendix 16.1.1 (Protocol for planned subjects in PK and Pharmacodynamic Analysis Set)
Abbreviations: eCRF = electronic case report form; ITT = Intention-to-Treat; FLIPI2 = Follicular Lymphoma International Prognostic Index 2.
Percentages were calculated using the number of subjects randomized as the denominator (n/N*100).
n: number of subjects within the category
Intention-To-Treat (ITT) Analysis Set: This included all randomized subjects;
For the definition of the different analysis sets, please refer to Section 9.7.1.2.
$ - The reason for this analysis set is captured at Section 10.4.2.

Outcomes and estimation

Primary endpoint: BORR up to week 28

The primary endpoint, i.e. BOR up to week 28 based on central radiology review in the ITT population, was N=130 (80.25%) in the DRL_RI group, and N=123 (79.35%) in the MabThera group. The analysis of BORR showed an estimated difference of 0.89%, with a 95% CI of (-8.05%, 9.93%), which fell entirely within the pre-specified equivalence margin of ±17%.

Table 22 - Main Analysis: Difference in Best Overall Response Rate (BORR) up to Week 28 Based on Central Radiology Review (ITT Analysis Set)

Treatment	BORR, n (%)	90% CI	95% CI
DRL_RI (N=162)	130 (80.25)	74.39, 85.25	73.27, 86.08
MabThera (N=155)	123 (79.35)	73.28, 84.57	72.12, 85.43
DRL_RI - MabThera (Difference in BORR)	0.89%	-6.67, 8.48	-8.05, 9.93

Percentages were calculated using the number of subjects in the ITT Analysis Set as the denominator (n/N*100). The BORR was defined as the proportion of subjects who achieved complete response, partial response, or complete response unconfirmed up to Week 28 based on central radiology review in accordance with the response criteria for malignant lymphoma (Cheson 1999) [13].

Confidence intervals were calculated using unstratified exact score method (Chan 1999)[16] with treatment as an explanatory variable and BOR as a response.

The prespecified equivalence margin was ±0.17 (±17%).

Abbreviations: BOR = best overall response; BORR = best overall response rate; CI = confidence interval; ITT = Intent-to-Treat; n = number of subjects in a specific category; N = Number of subjects in the ITT Analysis Set.

Source: Study RI-01-006 Primary CSR-28 January 2023 Table 14.2.1.2.1 (Section 5.3.5.1.1).

For the PPS, based on *central radiology* review, the BORR up to Week 28 and 95% CIs was 80.4% (95% CI, 73.3 to 86.3) for the DRL_RI group and 79.9% (95% CI, 72.5 to 86.0) for the MabThera group. The difference of BORR between the DRL_RI group and MabThera group was 0.51% and 95% CI was -8.54, 9.64, thus also meeting the equivalence criteria.

Table 23 - Difference in BORR up to Week 28 Based on Central Radiology Review (Per Protocol Analysis Set)

Treatment	BORR, n (%)	90% CI	95% CI
DRL_RI (N=158)	127 (80.38)	74.45, 85.43	73.32, 86.26
MabThera (N=149)	119 (79.87)	73.70, 85.12	72.52, 85.98
DRL_RI - MabThera (Difference in BORR, %)	0.51%	-7.21, 8.20	-8.54, 9.64

Source: Study RI-01-006 Primary CSR-28 January 2023 Table 14.2.1.2.9 (Section 5.3.5.1.1).

Summary of BOR

A best response of CR was observed in 34.0% subjects in the DRL_RI group and 35.5% subjects in the MabThera group and a best response of PR was observed in 39.5% subjects in the DRL_RI group and 32.9% subjects in the MabThera group. A best response of CRu was observed in 6.8% subjects in the DRL_RI group and 11.0% subjects in the MabThera group.

Table 24 - Summary of Best Overall Response (BOR) up to Week 28 Based on Central Radiology Review (ITT Analysis Set)

	Statistics	DRL_RI (N=162)	MabThera® (N=155)	Overall (N=317)
Granular				
Complete response (CR)	n (%)	55 (34.0)	55 (35.5)	110 (34.7)
Unconfirmed complete response (CRu)	n (%)	11 (6.8)	17 (11.0)	28 (8.8)
Partial response (PR)	n (%)	64 (39.5)	51 (32.9)	115 (36.3)
Stable disease (SD)	n (%)	28 (17.3)	26 (16.8)	54 (17.0)
Progressive disease (PD)	n (%)	2 (1.2)	4 (2.6)	6 (1.9)
Unknown	n (%)	2 (1.2)	2 (1.3)	4 (1.3)
Binary				
Responder (CR + CRu + PR)[1]	n (%)	130 (80.2)	123 (79.4)	253 (79.8)
	95% CI	73.3, 86.1	72.1, 85.4	75.0, 84.1
Non-responder (SD, PD or Unknown)	n (%)	32 (19.8)	32 (20.6)	64 (20.2)
Complete Response Rate				
Responder (CR)[2]	n (%)	55 (34.0)	55 (35.5)	110 (34.7)
	95% CI	26.7, 41.8	28.0, 43.6	29.5, 40.2
Non-complete responder (CRu, PR, SD, PD or Unknown)	n (%)	107 (66.0)	100 (64.5)	207 (65.3)

Secondary endpoints

Overall Response Rate at Week 12 and Week 28 Based on Central Radiology Review

Table 25 - Summary of Overall and Complete Response at Weeks 12, 28 Based on Central Radiology Review (ITT Analysis Set)

Visit/Overall Response	Statistics	DRL_RI (N=162)	MabThera® (N=155)	Overall (N=317)
Week 12				
Complete response (CR)	n (%)	33 (20.4)	33 (21.3)	66 (20.8)
Unconfirmed Complete response (CRu)	n (%)	4 (2.5)	7 (4.5)	11 (3.5)
Partial response (PR)	n (%)	64 (39.5)	59 (38.1)	123 (38.8)
Stable disease (SD)	n (%)	55 (34.0)	47 (30.3)	102 (32.2)
Progressive disease (PD)	n (%)	3 (1.9)	4 (2.6)	7 (2.2)
No Evidence of Disease (NED)	n (%)	0	0	0
Unknown	n (%)	1 (0.6)	2 (1.3)	3 (0.9)
Missing	n (%)	2 (1.2)	3 (1.9)	5 (1.6)
Overall Response Rate				
Responder (CR + CRu + PR)[a]	n (%)	101 (62.3)	99 (63.9)	200 (63.1)
	95% CI	54.4, 69.8	55.8, 71.4	57.5, 68.4
Non-Responder	n (%)	61 (37.7)	56 (36.1)	117 (36.9)
Complete Response Rate				
Responder (CR)[b]	n (%)	33 (20.4)	33 (21.3)	66 (20.8)
	95% CI	14.5, 27.4	15.1, 28.6	16.5, 25.7
Non-complete Responder	n (%)	129 (79.6)	122 (78.7)	251 (79.2)
Week 28				
Complete response (CR)	n (%)	53 (32.7)	53 (34.2)	106 (33.4)
Unconfirmed Complete response (CRu)	n (%)	11 (6.8)	15 (9.7)	26 (8.2)
Partial response (PR)	n (%)	58 (35.8)	46 (29.7)	104 (32.8)
Stable disease (SD)	n (%)	16 (9.9)	17 (11.0)	33 (10.4)
Progressive disease (PD)	n (%)	13 (8.0)	6 (3.9)	19 (6.0)
No Evidence of Disease (NED)	n (%)	0	0	0
Unknown	n (%)	5 (3.1)	2 (1.3)	7 (2.2)
Missing	n (%)	6 (3.7)	16 (10.3)	22 (6.9)
Overall Response Rate				
Responder (CR + CRu + PR)[a]	n (%)	122 (75.3)	114 (73.5)	236 (74.4)
	95% CI	67.9, 81.7	65.9, 80.3	69.3, 79.2
Non-Responder	n (%)	40 (24.7)	41 (26.5)	81 (25.6)
Complete Response Rate				
Responder (CR)[b]	n (%)	53 (32.7)	53 (34.2)	106 (33.4)
	95% CI	25.6, 40.5	26.8, 42.2	28.3, 38.9
Non-complete Responder	n (%)	109 (67.3)	102 (65.8)	211 (66.6)

Complete Response Rate at Months 7 (Week 28)

Based on central radiology review, the CRR at Week 12 with 95% CIs was 20.4% (14.5 to 27.4) for the DRL_RI group and 21.3% (15.1 to 28.6) for the MabThera group (see also table above).

Based on central radiology review, the CRR at Week 28 with 95% CIs was:

- 32.7% (25.6 to 40.5) for the DRL_RI group
- 34.2% (26.8 to 42.2) for the MabThera group

Complete Response Rate as a Best Response up to Week 28

Based on central radiology review, the CRR as a best response up to Week 28 and 95% CIs in the ITT Analysis Set was:

- 34.0% (95% CI, 26.7 to 41.8) for the DRL_RI group
- 35.5% (95% CI, 28.0 to 43.6) for the MabThera group

Duration of response Duration of response (DOR) data until a cut-off date not earlier than the date of the latest Week 28 evaluation conducted for any study subject was analysed.

Duration of response until cut-off date (21 September 2021) for ITT population

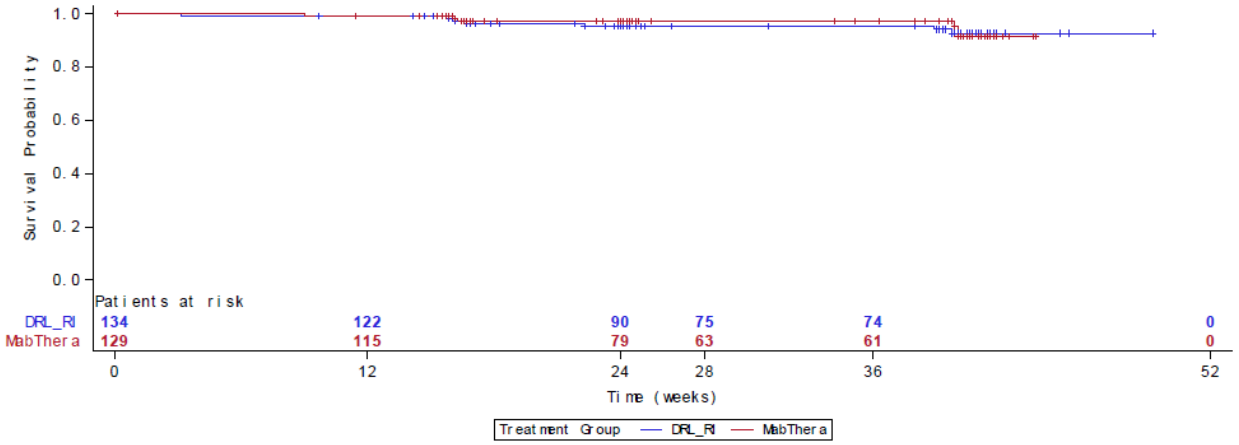
The median DOR was found to be not evaluable for both the treatment groups. The minimum DOR was 0.1 week in both the DRL_RI group and MabThera group. The maximum DOR was 49.3 weeks in the DRL_RI group and 43.7 weeks in the MabThera group.

Of 134 subjects who had CR, CRu or PR in DRL_RI arm, seven subjects (5.2%) had died or progressed until cut-off date of this CSR; in case of Mabthera arm of the 129 subjects who had CR, CRu or PR, six subjects (4.7%) had died or progressed until cut-off date of this CSR.

Table 26 - Duration of Response until cut-off date Based on Central Radiological Review (ITT Analysis Set)

	DRL RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with CR, CRu or PR	134	129	263
No. of subjects with CR, CRu or PR that died or progressed	7 (5.2)	6 (4.7)	13 (4.9)
No. of subjects censored	127 (94.8)	123 (95.3)	250 (95.1)
Estimated duration of response rate at			
Week 12 (95% CI)	0.99 (0.98, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 1.00)
Week 28 (95% CI)	0.96 (0.92, 0.99)	0.97 (0.94, 1.00)	0.96 (0.94, 0.99)
Week 36 (95% CI)	0.96 (0.92, 0.99)	0.97 (0.94, 1.00)	0.96 (0.94, 0.99)
Week 52 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Duration of response (weeks)			
N	134	129	263
Median	NE	NE	NE
95% CI**	NE, NE	NE, NE	NE, NE
25th,75th percentile	NE, NE	NE, NE	NE, NE
Min, max	0.1, 49.3	0.1, 43.7	0.1, 49.3

Figure 12 - Kaplan-Meier Plot for Duration of Response Based on Central Radiological Review (ITT Analysis Set)



Source: Figure 14.2.2.4
Abbreviation: CR = complete response; Cru = unconfirmed complete response; CSR = Clinical Study Report; EOS = End of Study; ITT = Intent to Treat; PD=Progressive Disease; PR = partial response
Duration of response 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 EOS or data cut-off. Subjects continuing without PD or death due to underlying cancer will be censored at the date of their last adequate tumor assessment.

At week 52 (EOS), the median DOR was found to be not evaluable for both the treatment groups. The minimum DOR was 0.1 week in both the DRL_RI and MabThera groups. The maximum DOR was 49.3 weeks in the DRL_RI group and 43.7 weeks in the MabThera group.

Table 14.2.2.4 Duration of Response Based on Central Radiological Review (ITT Analysis Set)

	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with CR, CRu or PR	134	130	264
No. of subjects with CR, CRu or PR that died or progressed	8 (6.0)	10 (7.7)	18 (6.8)
No. of subjects censored	126 (94.0)	120 (92.3)	246 (93.2)
Estimated duration of response rate at			
Week 12 (95% CI)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Week 28 (95% CI)	0.95 (0.91, 0.99)	0.97 (0.95, 1.00)	0.96 (0.94, 0.99)
Week 36 (95% CI)	0.95 (0.91, 0.99)	0.97 (0.95, 1.00)	0.96 (0.94, 0.99)
Week 52 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Progression-Free Survival

Based on central radiology review, the estimated PFS rate with 95% CI at Week 28 was:

- 0.79 (0.67 to 0.91) in the DRL_RI group
- 0.91 (0.86 to 0.96) in the MabThera group

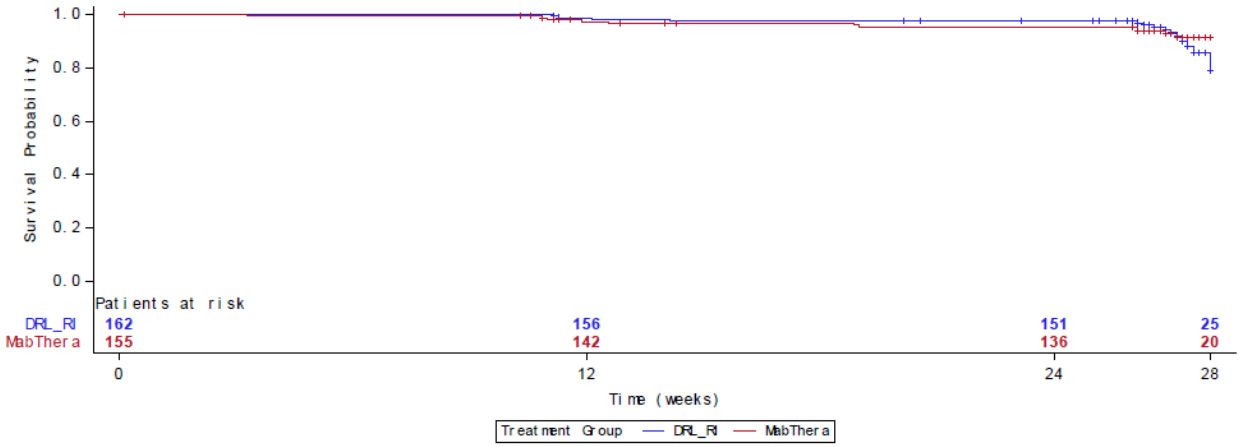
The median PFS at Week 28 was not evaluable in both the treatment groups.

Table 27 - Progression-Free Survival Based on Central Radiology Review (ITT Analysis Set)

	DRL RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with PD or death	15 (9.3)	11 (7.1)	26 (8.2)
No. of subjects censored	147 (90.7)	144 (92.9)	291 (91.8)
Estimated progression free survival rate at			
Week 12 (95% CI)	0.99 (0.97, 1.00)	0.97 (0.95, 1.00)	0.98 (0.97, 1.00)
Week 28 (95% CI)	0.79 (0.67, 0.91)	0.91 (0.86, 0.96)	0.85 (0.77, 0.92)
Progression-free survival (weeks)			
N	162	155	317
Median	NE	NE	NE
95% CI**	NE, NE	NE, NE	NE, NE
25th,75th percentile	NE, NE	NE, NE	NE, NE
Min, max	0.1, 28.0	0.1, 28.0	0.1, 28.0

Source: Listing 16.2.6.3
Abbreviations: CI = confidence interval; ITT = Intent to Treat; max = maximum; min = minimum; No. = number; PD = progressive disease; CSR = clinical study report
n: The number of subjects in a specific category; N: The number of subjects in the ITT Analysis Set; NE = Not Estimable.
Percentages were calculated using the number of subjects in the ITT Analysis Set as the denominator (n/N*100).
** 95% CI was computed using Brookmeyer Crowley method.
Progression-free survival defined as the time from date of randomisation to the date of documented PD (PD from Imaging shared through central imaging data) or death due to any cause.
Subjects who have not progressed or died have been censored at the last adequate tumor assessment date.
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.

Figure 13 - Kaplan-Meier Plot for Progression Free Survival Based on Central Radiology Review (ITT Analysis Set)



Source: Figure 14.2.2.1
Abbreviation: ITT = Intent to Treat; CSR = Clinical Study Report; PD=Progressive Disease
Progression-free survival defined as the time from date of randomization to the date of documented PD (PD from Imaging shared through central imaging data) or death due to any cause.
Subjects who are not progressed, not died, will be censored at the last adequate tumor assessment date.
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.

At Week 52 (EOS), the estimated PFS rate based on central radiology review with 95% CI was 0.82 (0.75 to 0.89) in the DRL_RI group and 0.84 (0.77 to 0.90) in the MabThera group. Based on central radiology review, the median PFS at Week 52 (EOS) was not evaluable in both the treatment groups.

Table 14.2.2.1 Progression-Free Survival Based on Central Radiology Review (ITT Analysis Set)

	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with PD or death	24 (14.8)	22 (14.2)	46 (14.5)
No. of subjects censored	138 (85.2)	133 (85.8)	271 (85.5)
Estimated progression free survival rate at			
Week 12 (95% CI)	0.99 (0.97, 1.00)	0.97 (0.95, 1.00)	0.98 (0.97, 1.00)
Week 28 (95% CI)	0.91 (0.86, 0.95)	0.92 (0.87, 0.96)	0.91 (0.88, 0.95)
Week 36 (95% CI)	0.90 (0.85, 0.94)	0.92 (0.87, 0.96)	0.91 (0.87, 0.94)
Week 52 (95% CI)	0.82 (0.75, 0.89)	0.84 (0.77, 0.90)	0.83 (0.78, 0.88)

Overall Survival

Table 28 - Overall Survival (ITT Analysis Set)

	DRL RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with death	1 (0.6)	0 (0.0)	1 (0.3)
No. of subjects censored	161 (99.4)	155 (100.0)	316 (99.7)
Estimated overall survival rate at			
Week 12 (95% CI)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Week 28 (95% CI)	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)
Overall survival (Weeks)			
N	162	155	317
Median	NE	NE	NE
95% CI**	NE, NE	NE, NE	NE, NE
25th,75th percentile	NE, NE	NE, NE	NE, NE
Min, max	1.6, 28.0	0.6, 28.0	0.6, 28.0

Source: Listing 16.2.6.4
Abbreviations: CI = confidence interval; CSR = Clinical Study Report; ITT = Intent to Treat; max = maximum; min = minimum. No. = number.
n: The number of subjects in a specific category; N: The number of subjects in the ITT Analysis Set; NE = Not Estimable.
Percentages were calculated using the number of subjects in the ITT Analysis Set as the denominator (n/N*100).
** 95% CI was computed using Brookmeyer-Crowley method.
Overall survival is defined as the time from date of randomisation to date of death due to any cause up to week 28.
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.

At Week 52 (EOS), the estimated OS rate based on central radiology review with 95% CI was 0.98 (0.96 to 1.00) in the DRL_RI group and 0.99 (0.97 to 1.00) in the MabThera group. Based on central radiology review, the median OS was not evaluable in both the treatment groups. The minimum OS was 1.6 weeks in the DRL_RI group and 0.6 week in the MabThera group.

Table 14.2.2.2 Overall Survival (ITT Analysis Set)

	DRL_RI (N=162) n (%)	MabThera® (N=155) n (%)	Overall (N=317) n (%)
No. of subjects with death	3 (1.9)	2 (1.3)	5 (1.6)
No. of subjects censored	159 (98.1)	153 (98.7)	312 (98.4)
Estimated overall survival rate at			
Week 12 (95% CI)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Week 28 (95% CI)	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)
Week 36 (95% CI)	0.99 (0.97, 1.00)	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)
Week 52 (95% CI)	0.98 (0.96, 1.00)	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)

Exploratory endpoints

Overall response rate based on the Lugano criteria for those subjects with available PET data

Assessment by Lugano 2014 criteria was available for 49.8 % of subjects of all randomized subjects.

A total of 79.1% of the subjects in Lugano assessment population set had concordance between Cheson 1999 and Lugano criteria for BOR response up to Week 28.

Table 29 - Summary of Best Overall Response (BOR) Rate (Lugano 2014) up to Week 28 Based on Central Radiology Review (ITT Analysis Set with PET data available)

Overall Response	Statistics	DRL_RI (N=74)	MabThera® (N=84)	Overall (N=158)
Granular				
Complete response(CR)	n (%)	32 (43.2)	43 (51.2)	75 (47.5)
Partial response(PR)	n (%)	24 (32.4)	19 (22.6)	43 (27.2)
Stable disease(SD)	n (%)	6 (8.1)	8 (9.5)	14 (8.9)
Progressive disease(PD)	n (%)	1 (1.4)	2 (2.4)	3 (1.9)
Unknown	n (%)	11 (14.9)	12 (14.3)	23 (14.6)
Binary				
Responder (CR + PR)[1]	n (%)	56 (75.7)	62 (73.8)	118 (74.7)
	95% CI	64.3, 84.9	63.1, 82.8	67.2, 81.3
Non-responder	n (%)	18 (24.3)	22 (26.2)	40 (25.3)
Granular				
Complete response(CR)	n (%)	32 (43.2)	42 (51.2)	74 (47.4)
Partial response(PR)	n (%)	24 (32.4)	19 (23.2)	43 (27.6)
Stable disease(SD)	n (%)	6 (8.1)	8 (9.8)	14 (9.0)
Progressive disease(PD)	n (%)	1 (1.4)	2 (2.4)	3 (1.9)
Unknown	n (%)	11 (14.9)	11 (13.4)	22 (14.1)
Binary				
Responder (CR + PR)[1]	n (%)	56 (75.7)	61 (74.4)	117 (75.0)
	95% CI	64.3, 84.9	63.6, 83.4	67.4, 81.6
Non-responder	n (%)	18 (24.3)	21 (25.6)	39 (25.0)

Source: Listing 16.2.6.2a
Abbreviations: CI = confidence interval; PP = Per Protocol; BOR= Best Overall Response
n: The number of subjects in a specific category; N: The number of subjects in the PP Analysis Set with available PET.
Percentages were calculated using the number of subjects in the PP Analysis Set with available PET as the denominator (n/N*100). The 95% CI was calculated using exact binomial method with treatment as an explanatory variable and BOR as a response.
[1]The proportion of responders in each treatment arm is defined as subjects who achieved complete response or partial response. The BOR was determined by using tumour response based on Lugano (2014) criteria only for those subjects with available positron emission tomography (PET) data.

Table 30 - Summary of Discrepancies Between Best Overall Response (Cheson 1999) and Best Overall Response (Lugano 2014) up to Week 28 Based on Central Radiology Review (ITT Analysis Set*)

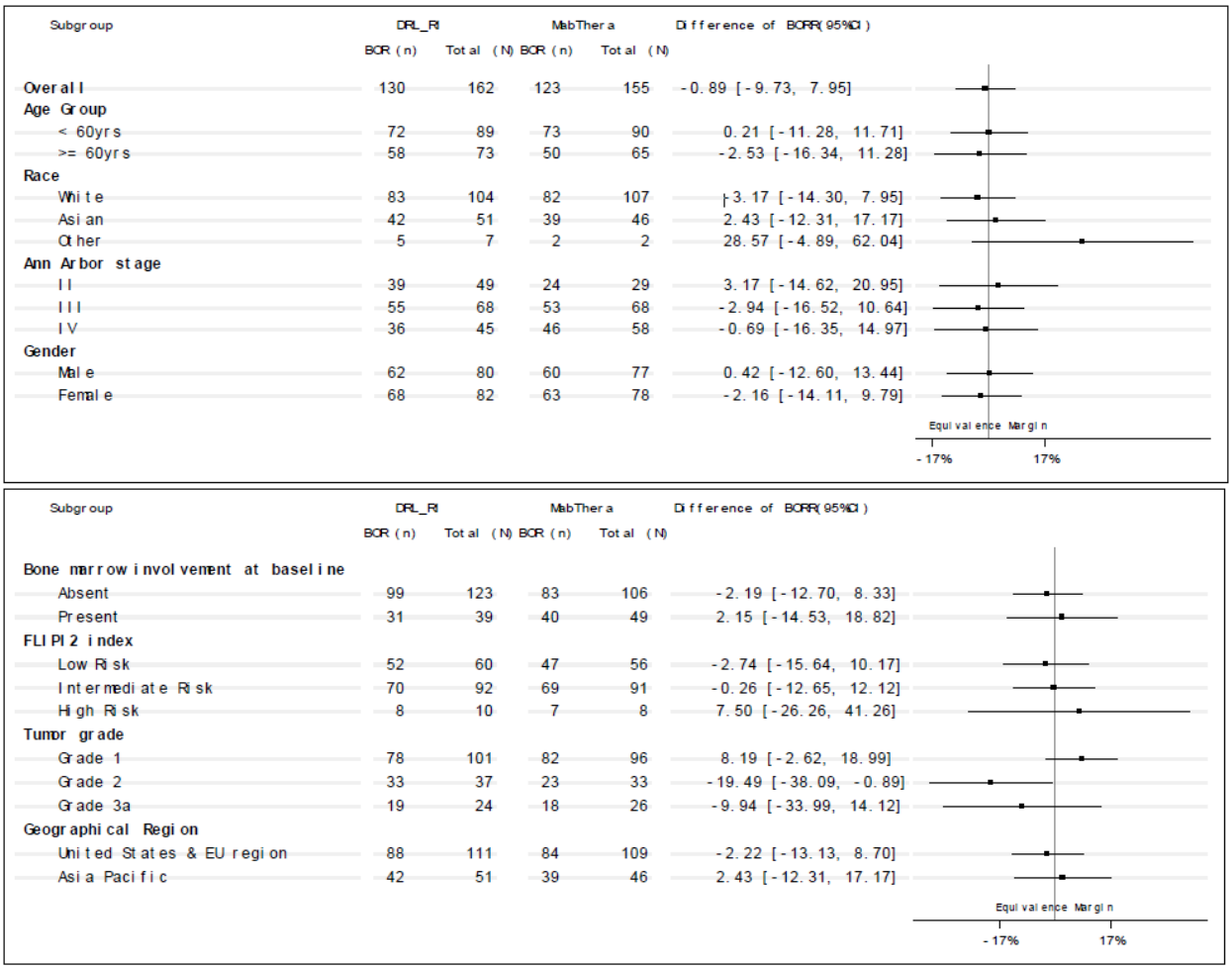
Concordance by subject between the Cheson 1999 & Lugano 2014 criteria classified best overall response	**DRL_RI (N=74) n (%)**	**MabThera® (N=84) n (%)**	**Overall (N=158) n (%)**
Concordant response class	58 (78.4)	67 (79.8)	125 (79.1)
Subjects classified as responders by Cheson 1999 criteria, but classified as non-responders by Lugano 2014 criteria	11 (14.9)	13 (15.5)	24 (15.2)
Subjects classified as non-responders by Cheson 1999 criteria, but classified as responders by Lugano 2014 criteria	5 (6.8)	4 (4.8)	9 (5.7)

Source: Table 14.2.3.2
Abbreviations: ITT = Intent to Treat
n: The number of subjects in a specific category; N: The number of subjects in the ITT Analysis Set with available PET.
Percentages were calculated using the number of subjects in the ITT Analysis Set with available PET as the denominator (n/N*100).
* Number of subjects included are subjects with available positron emission tomography (PET) data.

Ancillary analyses

Subgroup analyses by age, race, Ann Arbor stage, Gender, Bone marrow involvement at baseline, FLIPI2 index, tumour grade and geographical region were performed on the primary endpoint, BORR up to week 28.

Table 31 - Forest Plot for Subgroup Analysis (EMA) of Difference in Best Overall Response (BOR) rate up to Week 28 Based on Central Radiology Review (ITT Analysis Set)



Source: Table 14.1.4.1, 14.1.4.2 and 14.2.1.2.1
Abbreviation: ITT = Intent to Treat; CI = confidence interval; BOR = Best Overall Response; BORR = Best Overall Response Rate
CIs are obtained by the unstratified exact score method (Chan 1999).
Races Aboriginal/Torres Strait Islander, Not Reported and Unknown are considered under other race.

Table 32 - Overall Response (ORR) rate at Week 28 Based on Central Radiology Review by Tumor Grades (ITT Analysis Set)

Subgroup Tumor Grade	Treatment	ORR, n (%)	90% CI	95% CI
Grade 1	DRL_RI (N=101)	73 (72.28)	64.02, 79.53	62.48, 80.72
	MabThera® (N=96)	76 (79.17)	71.18, 85.75	69.67, 86.79
Source: table 14.2.1.2.1 G				

Subgroup Tumor Grade	Treatment	ORR, n (%)	90% CI	95% CI
Grade 2	DRL_RI (N=37)	31 (83.78)	70.48, 92.69	67.99, 93.81
	MabThera® (N=33)	21 (63.64)	47.84, 77.50	45.12, 79.60
Grade 3a	DRL_RI (N=24)	18 (75.00)	56.53, 88.51	53.29, 90.23
	MabThera® (N=26)	17 (65.38)	47.38, 80.60	44.33, 82.79
Source: table 14.2.1.2.1 E				

Table 33 - Overall Response (ORR) rate at Week 52 Based on Central Radiology Review for subjects by Tumor Grade (ITT Analysis Set)

Subgroup Tumor Grade	Treatment	ORR, n (%)	90% CI	95% CI
Grade 1	DRL_RI (N=101)	69 (68.32)	59.87, 75.94	58.31, 77.22
	MabThera® (N=96)	68 (70.83)	62.26, 78.41	60.67, 79.67
Source: table 14.2.1.2.1 H				
Grade 2	DRL_RI (N=37)	30 (81.08)	67.38, 90.77	64.84, 92.04
	MabThera® (N=33)	21 (63.64)	47.84, 77.50	45.12, 79.60
Grade 3a	DRL_RI (N=24)	17 (70.83)	52.13, 85.43	48.91, 87.38
	MabThera® (N=26)	19 (73.08)	55.32, 86.62	52.21, 88.43
Source: table 14.2.1.2.1 F				

Table 34 - Summary of CR, CRu, PR and SD at Weeks 28 Based on Central Radiology Review (ITT Analysis Set)

Subgroup Tumor Grade	Overall Response	Statistics	DRL_RI (N=162)	MabThera® (N=155)
Grade 1	Complete response (CR)	n (%)	29 (17.9)	28 (18.1)
	Unconfirmed Complete response (CRu)	n (%)	9 (5.6)	10 (6.5)
	Partial response (PR)	n (%)	35 (21.6)	38 (24.5)
	Stable disease (SD)	n (%)	11 (6.8)	9 (5.8)

Table 35 - Analysis of the difference in BORR up to week 28 per tumor grade stratified for the factors where differences were observed between the treatment groups

Baseline Tumor grade	Baseline characteristic	DRL_RI (N = 101) BOR (%)	MabThera (N = 96) BOR (%)	Difference of BORR (90% CI)
Grade 1	**Bone marrow involvement**			
	Absent	59 (58.42)	51 (53.13)	5.29 (-6.62, 17.03)
	Present	19 (18.81)	31 (32.29)	-13.48 (-23.89, -2.32)
Grade 2	**Age Group**			
	<60 years	22 (59.46)	14 (42.42)	17.04 (-3.15, 36.18)
	≥60 years	11 (29.73)	9 (27.27)	2.46 (-16.05, 20.74)
	Baseline haemoglobin			
	< 120 gm/L	2 (5.41)	1 (3.03)	2.38 (-8.60, 13.23)
	≥ 120 gm/L	31 (83.78)	22 (66.67)	17.12 (-0.41, 35.17)
	FLIPI2 Index			
	Low risk	16 (43.24)	11 (33.33)	9.91 (-10.41, 29.52)
	Intermediate risk	15 (40.54)	11 (33.33)	7.21 (-13.23, 27.07)
	High risk	2 (5.41)	1 (3.03)	2.38 (-8.60, 13.23)
Grade 3a	**Baseline haemoglobin**			
	< 120 gm/L	2 (8.33)	4 (15.38)	-7.05 (-25.08, 9.64)
	≥ 120 gm/L	17 (70.83)	14 (53.85)	16.99 (-6.39, 39.52)
	Bone marrow involvement			
	Absent	16 (66.67)	14 (53.85)	12.82 (-11.73, 36.35)
	Present	3 (12.50)	4 (15.38)	-2.88 (-21.25, 15.19)
	Longest diameter of largest involved node for FLIPI2 score			
	< 6 cm	19 (79.17)	18 (69.23)	9.94 (-11.73, 30.67)
	≥ 6 cm	0	0	
	FLIPI2 Index			
	Low risk	9 (37.50)	5 (19.23)	18.27 (-3.51, 40.04)
	Intermediate risk	8 (33.33)	12 (46.15)	-12.82 (-36.35, 11.73)
	High risk	2 (8.33)	1 (3.85)	4.49 (-9.54, 19.93)

Source: Table 14.2.1.2.1.I; 14.2.1.2.1.J & 14.2.1.2.1.K

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 36 Summary of efficacy for trial RI-01-006

Title: A Randomised, Double-blind, Parallel-group, Phase III Study to Compare the Efficacy, Safety, and Immunogenicity of Proposed Rituximab Biosimilar (DRL_RI) with MabThera in Subjects with Previously Untreated, Stage II-IV, Cluster of Differentiation (CD)20-Positive, Low Tumour Burden Follicular Lymphoma			
Study identifier	RI-01-006		
Design	Phase III, randomized, multicentre, double-blind, parallel-group study in subjects with previously untreated, Stage II-IV, CD20-positive, LTB-FL. Eligible subjects were randomized to receive either DRL_RI or EU-approved MabThera®. Randomization was stratified by low-, medium-, and high-risk subjects using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2), as well as by tumour grade and geographical area (United States of America [USA], Europe and Asia Pacific region).		
	Duration of Screening:		Days -35 to -1
	Duration of Main Treatment:		Subjects received induction treatment with 375 mg/m^2 i.v. weekly followed by maintenance treatment of 375 mg/m^2 i.v. every 8 weeks starting at Week 12 until Week 36
	Duration of Follow-up:		After completion of the Maintenance Treatment Period, subjects were followed up till 52 weeks after the first dose of study drug (at Weeks 44 and 52). The presented data is for up to 28 weeks.
Hypothesis	Equivalence applying pre-specified symmetrical biosimilar margins ±0.17 (±17%).		
Treatments groups	***DRL_RI Group***		162 subjects were randomised to the DRL_RI group
	MabThera Group		155 subjects were randomised to the MabThera group
Endpoints and definitions	***Primary endpoint***	BORR	Best overall response rate (BORR), defined as the proportion of subjects in each treatment group that achieved a best overall response of either CR, CRu, or PR up to Week 28 based on central radiology review in accordance with the response criteria for malignant lymphoma (Cheson 1999)[i].
	Secondary endpoint (1)	ORR	Overall response rate (ORR) at Week 12 and Week 28 based on central radiology review in accordance with published response criteria for malignant lymphoma i.
	Secondary endpoint (2)	CRR	Complete response rate (CRR) at Week 28.
	Secondary endpoint (3)	CRR	Complete response rate (CRR) as a best response up to Week 28.

	Secondary endpoint (4)	DOR	Duration of response (DOR) defined as the time from date of the first documentation of tumour response (CR, CRu, or PR) to the date of first documentation of progressive disease (PD) or to death due to any cause up to 52 weeks/End of Study (EOS).
	Secondary endpoint (5)	PFS	Progression-free survival (PFS) defined as the time from date of randomization to the date of documented PD or death due to any cause.
	Secondary endpoint (6)	OS	Overall survival defined as the time from date of randomization to the date of death from any cause up to 52 weeks/ EOS.
	Exploratory endpoint	BORR	Overall response rate (ORR) based on the Lugano criteria[ii] for those subjects with available positron emission tomography (PET) data. Best Overall Response (BOR) (CR or PR) up to Week 28 based on central radiology review based on the Lugano criteria (Cheson 2014)[2] had been summarized using frequency and percentage with corresponding 95% CI by treatment group for subjects with PET data in the PP and ITT Analysis Set.
Database lock	21 September 2021.		

Results and Analysis

For the reporting in this CSR, data up to Week 28 are presented. For this Week 28 CSR analysis, DOR data until a cut-off date not earlier than the date of the latest Week 28 evaluation conducted for any study subject is in the analysis.

Analysis description	**Primary Analysis**		
Analysis population and time point description	The Per-Protocol Analysis Set (PPS) included all randomised subjects who: • Received at least one dose of study drug • Had measurable disease at Baseline as confirmed by central review • Had an at least one available valid response evaluation up to Week 28 (± 4 weeks) • No major protocol deviations that would significantly impact the primary efficacy endpoint. The Intention-To-Treat (ITT) Analysis Set included all randomized subjects. For EMA, the primary efficacy analysis was based on the PPS and ITT Analysis Set.		
Descriptive statistics and estimate variability	***Treatment group***	DRL_RI	MabThera
	Number of subjects	162 (ITT); 158 (PPS)	155 (ITT); 149 (PPS)
	BORR *n (%) (PPS)*	127 (80.38)	119 (79.87)
	95% Confidence interval	73.32, 86.26	72.52, 85.98
	BORR *n (%) (ITT)*	130 (80.25)	123 (79.35)
	95% Confidence interval	73.27, 86.08	72.12, 85.43
	ORR at Week 12 *n (%) (ITT)*	101 (62.3)	99 (63.9)
	95% Confidence interval	54.4, 69.8	55.8, 71.4
	ORR at Week 28 *n (%) (ITT)*	122 (75.3)	114 (73.5)
	95% Confidence interval	67.9, 81.7	65.9, 80.3
	CRR at Week 28 *n (%) (ITT)*	58 (35.8)	51 (32.9)

	95% Confidence interval	28.4, 43.7	25.6, 40.9
	CRR as a best response at Week 28 *n (%) (PPS)*	54 (34.2)	54 (36.2)
	95% Confidence interval	26.8, 42.1	28.5, 44.5
	CRR as a best response at Week 28 *n (%) (ITT)*	55 (34.0)	55 (35.5)
	95% Confidence interval	26.7, 41.8	28.0, 43.6
	DOR at Week 28 *(ITT)*	The median DOR was found to be not evaluable for both the treatment groups. The minimum DOR was 0.1 week in both the DRL_RI group and MabThera group. The maximum DOR was 24.6 weeks in the DRL_RI group and 20.4 weeks in the MabThera group Of 130 subjects who had CR, CRu or PR in DRL_RI arm, four subjects (3.1%) had died or progressed up to week 28; in case of MabThera arm of the 123 subjects (2.4%) who had CR, CRu or PR, three subjects had died or progressed prior to week 28 (Table 14.2.2.3).	
	DOR data until cut-off date *(ITT)*	The median DOR was found to be not evaluable for both the treatment groups. The minimum DOR was 0.1 week in both the DRL_RI group and MabThera group. The maximum DOR was 49.3 weeks in the DRL_RI group and 43.7 weeks in the MabThera group. Of 134 subjects who had CR, CRu or PR in DRL_RI arm, seven subjects (5.2%) had died or progressed until cut-off date of this CSR; in case of MabThera arm of the 129 subjects who had CR, CRu or PR, six subjects (4.7%) had died or progressed until cut-off date of this CSR. (Table 14.2.2.4).	
	Estimated PFS rate at Week 28 *(%) (ITT)*	0.79	0.91
	95% Confidence interval	0.67, 0.91	0.86, 0.96
	Estimated OS rate at Week 28 *(%) (ITT)*	0.99	1.00
	95% Confidence interval	0.98, 1.00	1.00, 1.00
	BORR based on the Lugano criteriaii ***up to Week 28,*** *n (%) (PPS)*	56 (75.7)	61 (74.4)
	95% Confidence interval	64.3, 84.9	63.6, 83.4
	BORR based on the Lugano criteriaii ***at Week 28,*** *n (%) (ITT)*	56 (75.7)	62 (73.8)
	95% Confidence interval	64.3, 84.9	63.1, 82.8
Effect estimate per comparison	***Primary endpoint***	***Comparison groups***	DRL_RI and MabThera

		Difference in BORR, % (PPS)	0.51 %
		95% Confidence interval	-8.54, 9.64
		Difference in BORR, % (ITT)	0.89%
		95% Confidence interval	-8.05, 9.93
Notes	As of 21 Sep 2022 (Data cut-off date): Of the 162 subjects receiving DRL_RI, a total of 19 subjects (11.7%) were discontinued during the study. Of the 19 subjects who discontinued from DRL_RI group, 4 subjects (2.5%) withdrew consent, 2 subjects (1.2%) discontinued due to AEs and 9 subjects (5.6%) discontinued due to other reasons (disease progression, except single subject). Three subjects (1.9%) died and 1 subject (0.6%) was withdrawn due to Investigator's decision. Of these 3 deaths, 2 subjects died while on treatment and one subject died posttreatment. Both the subjects who died on treatment were in the Maintenance Treatment Period; of which, one subject received 5 doses and other subject received 6 doses in this study. Of the 155 subjects receiving MabThera, a total of 26 subjects (16.8%) were discontinued during the study. Of the 26 subjects who discontinued from MabThera group, 4 subjects (2.6%) withdrew consent, 2 subject (1.3%) subject lost to follow-up, 4 subjects (2.6%) discontinued due to AEs and 13 subjects (8.4%) discontinued due to other reasons (disease progression, except single subject). Two subject (1.3%) died and 1 subject (0.6%) was withdrawn due to Investigator's decision. Of these 2 deaths, both the subjects died posttreatment.		
Analysis description	**Primary Analysis**: Two-sided 90% and 95% confidence intervals (CIs) for the difference in BOR up to Week 28 probability difference (DRL_RI minus MabThera) were obtained by the unstratified exact score method (Chan 1999)[iii] implemented in SAS Proc FREQ. For EMA, biosimilarity was concluded (i.e., the null hypothesis rejected) if the 95% CI is completely contained within the predefined interval (-0.17, 0.17).		
	Secondary Analysis: ***OR:*** Overall response (OR) by central review at Week 12 and at Week 28 was summarized using frequencies, percentages and corresponding 95% CIs by treatment group. ***CR:*** Complete response (CR) by central review at Week 28 was summarized using frequency, percentage and corresponding 95% CI by treatment group. ***PFS***: PFS by central review was 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 were summarized by treatment group. ***DOR and OS:*** DOR and OS were 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 were summarized by treatment group.		
	Exploratory Analysis: Best overall response (BOR) up to Week 28 based on central radiology review based on the Lugano criteriaii was summarized using frequency and percentage with corresponding 95% CI by treatment group for		

	subjects with PET data. A summary of any discrepancies between response designation via the 1999 IWG criteria (primary endpoint) and Lugano criteria was provided.

2.6.5.4. Clinical studies in special populations

Not applicable.

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.7. Supportive study

Study RI-01-003

Supportive efficacy data were derived from study RI-01-003, a randomized, multicentre, double-blind, parallel 3-way equivalence study comparing DRL_RI to MabThera and Rituxan in combination with stabilized doses of non-biological disease-modifying antirheumatic drugs (DMARDs) in patients with active RA with an inadequate response to methotrexate-based therapy. Patients received one single course of rituximab treatment with dosing on Day 1 and Day 15. Stratification factors were gender and region (e.g., countries/subcontinent).

Primary objective of the study was demonstrating PK bio-equivalence. Secondary efficacy endpoints were ACR20, ACR50, and ACR70, continuous variable DAS28 (Disease Activity Score in 28 Joints Using C-reactive Protein), change from baseline for Health Assessment Questionnaire Disability Index (HAQ-DI) and visual analogue scale (VAS).

For all the secondary endpoints of Study RI-01-003, there was no formal statistical hypothesis put forth, a priori. All efficacy endpoint analyses were performed for the PP and ITT Analysis Set.

276 patients were randomized to 1 of the 3 treatment arms (DRL_RI: 91, Rituxan: 92, MabThera: 93). A total of 240 (87%) patients (DRL_RI: 82 [90.1%], Rituxan: 79 [85.9%], MabThera 79 [84.9%]) completed Week 52 visit. A total of 14 (5.1%) patients discontinued prior to Week 52 and the primary reason for discontinuation were: lost to follow-up (6 [42.9%] patients), withdrawal of consent (3 [21.4%] patients), adverse events (2 [14.3%] patients), progressive or relapse disease (2 [14.3%] patients), and other (1 [7.1%] patient).

Table 37 Baseline and disease characteristics

Characteristics	Clinical StudyRI-01-003[a]		
	DRL_RI	Rituxan	MabThera
N	**91**	**92**	**93**
Mean Age (years)	44.1	44.0	45.5
Gender; n (%)			
Female	81 (89.0)	81 (88.0)	81 (87.1)
Male	10 (11.0)	11 (12.0)	12 (12.9)
N	**91**	**92**	**93**
Swollen Joints (28 Joint Count) (Mean no.)	12.4	11.0	11.1
Swollen Joints (66 Joint Count) (Mean no.)	16.2	13.5	13.5
Tender Joints (28 Joint Count) (Mean no.)	17.1	14.8	14.4
Tender Joints (68 Joint Count) (Mean no.)	24.2	20.5	18.6
C-reactive protein, mean	18.9 (mg/L)[b]	17.3 (mg/L)[b]	18.1 (mg/L)[b]
N	**88**	**87**	**87**
Baseline HAQ-DI score, mean	1.56[c]	1.47[c]	1.49[c]
DAS28, mean	6.04[c]	5.74[c]	5.77[c]

Efficacy Outcomes

ACR20, ACR50, ACR70

Table 38 - Statistical Analysis of ACR20, ACR50, and ACR70 at Week 24 (Per Protocol Analysis Set)

Endpoint	Treatment Group	N	n	Adjusted Response Rate (%)	Difference in Adjusted Response Rate (%) (DRL_RI - Rituxan)	Difference in Adjusted Response Rate (%) (DRL_RI - MabThera)	Difference in Adjusted Response Rate (%) (Rituxan - MabThera)	95% CI
ACR20 response	DRL_RI	82	59	72.0	2.8	-	-	(-11.18, 16.81)
	Rituxan	81	56	69.1	-	-	0.8	(-13.58, 15.15)
	MabThera	79	54	68.4	-	3.6	-	(-10.54, 17.73)
ACR50 response	DRL_RI	82	36	43.9	4.4	-	-	(-10.73, 19.52)
	Rituxan	81	32	39.5	-	-	-3.5	(-18.78, 11.72)
	MabThera	79	34	43.0	-	0.9	-	(-14.45, 16.18)
ACR70 response	DRL_RI	82	14	17.1	2.3	-	-	(-8.97, 13.49)
	Rituxan	81	12	14.8	-	-	-0.4	(-11.44, 10.69)
	MabThera	79	12	15.2	-	1.9	-	(-9.47, 13.24)

ACR20: At least 20% improvement in counts of tender, swollen joints and in three of the following: patient's assessment of pain, patient's global assessment of disease activity, patient's assessment of physical function, the physician's global assessment of disease activity, and acute phase reactant.

ACR50: At least 50% improvement in counts of tender, swollen joints and in three of the following: patient's assessment of pain, patient's global assessment of disease activity, patient's assessment of physical function, the physician's global assessment of disease activity, and acute phase reactant.

ACR70: At least 70% improvement in counts of tender, swollen joints and in three of the following: patient's assessment of pain, patient's global assessment of disease activity, patient's assessment of physical function, the physician's global assessment of disease activity, and acute phase reactant.

Adjusted Response rates for the treatment groups using the logistic regression analysis including treatment, gender and region as fixed effects and patients as random effect in the model.

Abbreviations: ACR: = American College of Rheumatology; CI = confidence interval; DRL_RI = Dr Reddy's rituximab; N = number of patients in the corresponding visit; n = number of responders.

Source: Study RI-01-003 CSR Part 1-Final-05 October 2017 Table 14.2.6.1(a), Table 14.2.6.1(b), and Table 14.2.6.1(c) (Section 5.3.3.2.1).

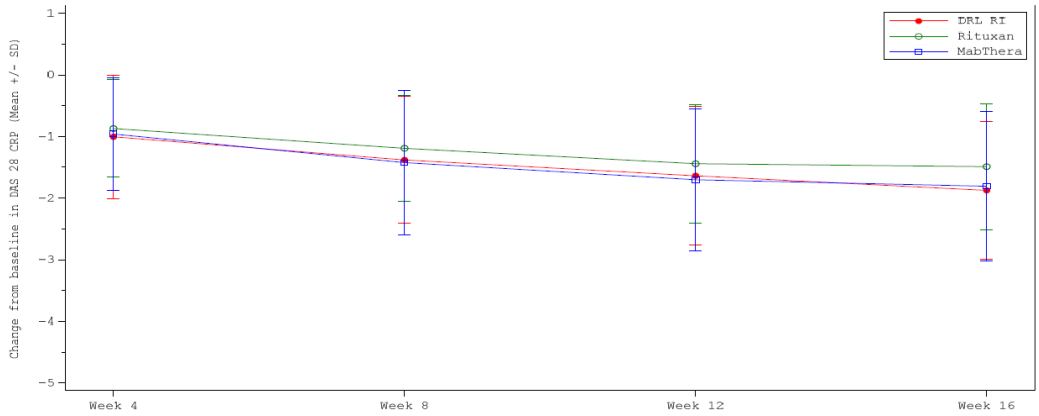
DAS-28-CRP

Table 39 - Statistical Analysis of Change from Baseline at Week 24 in DAS28-CRP (PP Population)

	DRL_RI (N=81)			Rituxan® N=81			MabThera® N=79			Mean Difference (SE)	95% CI
Endpoint	N	LS Mean	SE	N	LS Mean	SE	N	LS Mean	SE		
Change from Baseline	81	-1.63	0.13	81	-1.57	0.12	79	-1.78	0.12	NA	NA
DRL_RI/Rituxan	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.06 (0.14)	(-0.33, 0.21)
DRL_RI/MabThera	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.16 (0.15)	(-0.13, 0.44)
Rituxan/MabThera	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.21 (0.14)	(-0.06, 0.49)

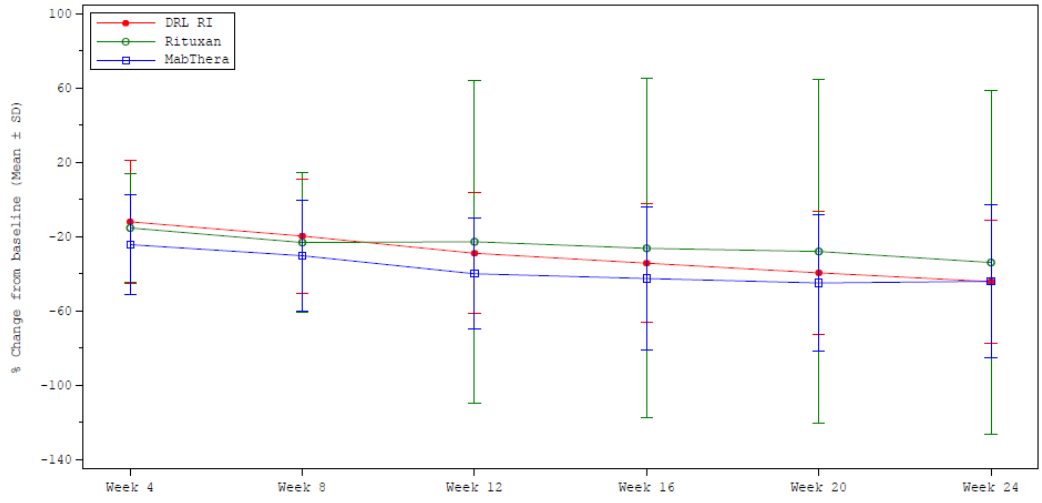
Abbreviations: GEE: Generalized Estimating Equation, N is the number of patients within each treatment arm under PP population; n is number of responder at week 24. SE: Standard Error.
The analysis of DAS28-CRP was based on a generalized estimating equation model where the response variable is mean change from baseline at each of the measured time points.
Baseline score, treatment, region, gender and time are included as a fixed factor in the model and the robust (sandwich) variance estimate is also used. Normal distribution and identity link function is used in the model. Exchangeable covariance matrix is used as correlation structure. 1010001 patient is not included as DAS28-CRP is not evaluated at Week 24.
Source: Table 14.2.5.3, Listing 16.2.6.5 and 16.2.6.6

Figure 14 - Mean Change from Baseline in DAS28-CRP by Visit and Treatment (PD population)



HAQ-DI

Figure 15 - Percentage Change from Baseline Mean ± SD in ACR Score (Response)-HAQ-DI (PP Population)



Abbreviations: SD: Standard deviation, HAQ-DI: Health Assessment Questionnaire Disability Index
The geometric mean calculation for change from baseline columns are based on the ratio of visit value to baseline value.
Source: Figure 14.3.2.1

VAS

Pain and disease activity were comparably reduced at Week 24 in all 3 treatment arms.

2.6.6. Discussion on clinical efficacy

Dose response studies have not been conducted to support this MAA. This is acceptable for a biosimilar application.

Study RI-01-06, a randomised, double-blind, parallel-group, ongoing Phase 3 study conducted in patients with histologically confirmed Grade 1-3a, CD20-positive FL was considered pivotal for demonstrating therapeutic equivalence in terms of efficacy.

Supportive efficacy data were derived from study RI-01-003, a randomised, double-blind, parallel 3-way equivalence study comparing DRL_RI to MabThera and Rituxan, which is the pivotal PK/PD bioequivalence study in patients with active RA. The study was not designed for formal statistical comparison of efficacy endpoints.

Design and conduct of clinical studies

Pivotal efficacy study RI-01-006

Choice of Model

The pivotal efficacy study (RI-01-006) enrolled adult patients with histologically confirmed Grade 1-3a, previously untreated, CD20-positive, LTB-FL (low-tumour burden follicular lymphoma) as per GELF based criteria. Subjects must have had a centrally-confirmed diagnosis prior to randomisation and be asymptomatic for systemic or B-symptoms. Subjects having received any prior therapy for FL including but not limited to chemotherapy and radiotherapy were excluded from the study.

The chosen indication LTB-FL – although not an approved indication of MabThera – is considered sensitive for detecting potential differences between the biosimilar DRL_RI and the reference medicinal product MabThera, as rituximab was administered as monotherapy and the comparability exercise was not confounded by concomitant treatment as well as advanced disease. The choice of model was also supported by CHMP (EMA/CHMP/SAWP/720016/2017). In addition, current treatment guidelines (eg. ESMO Annals of Oncology 32 (Issue 3): P298-308, 2020) consider rituximab treatment as an option for LTB-FL along with watchful waiting without active treatment or radiotherapy.

Study design

The choice of a double-blind, parallel group, randomised design is considered adequate for a comparability trial. The overall study duration (4-week Induction Treatment Period, a Maintenance Treatment Period of 24 weeks and a Follow-up Period of 8 weeks) is considered acceptable.

The eligible population consisted of patients with a rather mild form of follicular lymphoma (LTB-FL) without high disease burden and prior treatment thereby limiting potentially confounding factors. Moreover, the choice of in- and exclusion criteria (e.g. exclusion of patients with B symptoms or LDH levels above the upper normal limits) ensured the selection of a homogenous population appropriate for rituximab treatment. An independent review was conducted to confirm that the subject's Baseline/Screening imaging met the inclusion criteria.

The posology approved for the treatment of FL in the relapsed/refractory setting (without chemotherapy) has been chosen (375 mg/m^2 of body surface area for up to 8 cycles). This regimen was also used in the Ardeshna trial, which was used as reference study for LTB-FL.

Randomisation was stratified by 3 factors with in total 18 strata – FLIPI2 low-, medium-, high-risk; tumour grade (Grade 1-2 vs. 3a) and geographical region (US, Europe, Asia-Pacific region) – many of which with very low patient counts. For example, in the US there was only one subject enrolled (and hence all US-related strata are essentially empty). Also subjects at high risk and with tumour grade 3a were hardly enrolled. This counteracts the desire to balance groups for prognostic (or potentially predictive) factors and is not considered optimal. While the proposed stratification criteria are supported, a reduced number of strata would have been beneficial.

Endpoints

The primary endpoint was BORR, defined as the proportion of subjects in each treatment group that achieve a best overall response (BOR) of either complete response (CR), unconfirmed complete response (CRu), or partial response (PR) up to Month 7 (Week 28) based on central radiology review in accordance with the International Working Group (IWG) response criteria for malignant lymphoma (Cheson 1999).

Central review of the primary endpoint (by two independent reviewers) is endorsed.

In general, ORR is considered a sensitive parameter to detect differences and to document comparability between the DRL_RI and the reference medicinal product. In scientific advice EMA/CHMP/SAWP/720016/2017 CHMP recommended ORR at week 28 as primary endpoints, which was originally chosen as primary endpoint. However, with Protocol Amendment 4 (Version 5.0/27 Oct 2021), the primary endpoint was changed to BORR up to week 28. Although the initially chosen primary endpoint would have been preferred, as it is considered more sensitive with regards to the comparability exercise, it is acknowledged that ORR at week 28 was maintained as secondary endpoint. Upon request, the Applicant clarified that the endpoint was changed to limit the impact of COVID-19 on the trial results and to reduce the amount of missing data in the primary endpoint. If only one of the two visits at week 14 and 28 was missed or not conducted in the specified time frame, the result of the other visit was to be used as outcome. At the same time the visit window was widened from ±2 to ± 4 weeks to additionally alleviate the impact of COVID-19.

As for choice of response criteria, CHMP recommended the use of Lugano criteria as these criteria include PET-CT as standard parameter improving the assessment of responses. The Applicant deviated from this recommendation by using Cheson-1999 response criteria. This approach was justified by the choice of the reference study (Ardeshna et. Al), which was used as historical study for the justification of the equivalence margin and the calculation of the study size, as well as the feasibility of PET-CT scans at the study centres. It is however acknowledged that Lugano criteria were applied to a subgroup of patients with available PET-CT results were available (N=158 (49.8%)). Data have been provided with this submission along with an assessment of concordance between Cheson-1999 and Lugano criteria.

Secondary endpoints including but not limited to complete response rates, one-year OS and PFS as well as exploratory endpoints such as B-cell depletion are considered reasonable endpoints in the context of a comparability trial.

Equivalence criteria

There is only one study (Ardeshna et al) which forms the basis for the prespecified equivalence margin (±17%) for BORR.

A clinical justification for the chosen equivalence margin, i.e. a rationale that a difference of ±17% from the expected BORR is irrelevant from a clinical point of view, has not been provided. However, the Applicant provided a table displaying (B)ORR data from the reference study as well as from historical data with comparable response rates to study RI-01-006.

Of note: With Protocol Amendment 4 (Version 5.0/27 Oct 2021) a change of equivalence margin from ±16 % to ±17% occurred (see also below).

Statistics

A blinded sample size re-assessment (BSSR) was pre-specified for RI-01-006. The applicant showed in a simulation study and in line with the literature (e.g. Friede et al., DOI: 0.1002/bimj.200610373) that no type 1 error inflation is to be expected in the case of re-estimating the response rate in a blinded fashion. The BSSR is hence overall considered acceptable.

It is noted, though, that in parallel to the BSSR the primary endpoint was changed from ORR at week 28 to BOR up to week 28 and the equivalence margin was changed as well. These changes were not pre-specified via an SAP or protocol amendment but only via the final BSSR plan (01 Sept 2021) and finally implemented together with the updated sample size after BSSR in the protocol and SAP. Additionally, the Applicant provided documentation of a meeting with FDA on 02 Jul 2021 where these changes were discussed as well and to which FDA in principle agreed.

Statistical analysis methods are overall considered adequate. The rationale to primarily use an unstratified analysis are not understood. However, it is acknowledged that sensitivity analyses using a stratified MH-method were pre-specified. Additional sensitivity analyses and dedicated estimands were specified in the protocol and/or the SAP. The description of the estimand is considered very technical and mainly centred around multiple imputation (MI) approaches to estimate treatment policy or hypothetical estimands. In many circumstances it is difficult to judge whether the assumptions and choices made are adequate for the situation of a biosimilar development. Given the very consistent results between the primary analysis with sensitivity analyses and the estimand based analyses, the specifics are considered of minor relevance for the given procedure. In future procedures more weight should be put on the clinical interpretation and justification of the estimand in the light of the biosimilar development (i.e. maximising assay sensitivity).

Conduct of the trial

The protocol was amended four times. Major changes were introduced with Protocol Amendment 4 – the study was ongoing for 2 years then - with a change of primary endpoint from ORR at week 28 to BORR up to week 28 and a change of equivalence margin from ±16 % to ±17%. In parallel to this change the BSSR was conducted (see above). It is noted that according to the BSSR plan, personnel from the Applicant had access to the BSSR plan and even more problematic, leading personnel from the Applicant (i.e., head of clinical development, head of clinical sciences, and group lead biostatistics) were involved in the DMC meeting for BSSR. This might have negatively impacted blinding of trial results.

The number of protocol deviations was comparable between the treatment arms but overall rather high. This may be attributed to the Applicant`s approach of capturing deviations but also due to the COVID-19 pandemic and mis-stratification of FLIPI2 risk category. For the latter additional analyses were conducted, that were similar to those of the primary endpoint (BORR difference 0.15%).

Regarding minor protocol deviations, a relatively high number of patients had deviations classified as "IP admin/study treat" (DRL_RI 72.2%, MabThera 71.0%). These were mainly attributed to a mismatch off IP volume administered and the protocol required dose. According to the Applicant correctness of the administration of intended and protocol required doses were confirmed by the CRA and the principal investigators.

Data set

The final and complete CSR for study RI-01-006 including the updated week 52 data for DOR, PFS and OS set was submitted with the responses to the LoQ.

Supportive study RI-01-003

The second clinical study was conducted in a non-oncology indication, which is deemed adequate with regards to demonstrating PK/PD equivalence. Study RI-01-003 enrolled patients with active rheumatoid arthritis who received rituximab in combination with stabilised doses of non-biological DMARD therapy, which is deemed an adequate choice of model for demonstrating PK equivalence between DRL_RI and MabThera. Moreover, it allows assessment of similarity of DRL_RI and MabThera in a different non-oncology indication thereby supporting extrapolation to all indications of MabThera.

The randomised, double-blind design of a 3-way comparison between biosimilar, EU and US product is a common and acceptable study design used for demonstrating PK/PD equivalence. The chosen stratification factors gender and region (e.g., countries/subcontinent) are reasonable. Dose and regimen of rituximab treatment was in accordance with the approved regimen for Rheumatoid Arthritis (1000 mg of the study drug, one each on Day 1 and Day 15). To maintain the blinding, only pharmacists responsible for preparing the study blind were unblinded. This is supported.

Patients were on MTX, 15 to 25 mg per week when given alone or 10 to 25 mg per week in combination with additional non-biologic DMARD(s) (hydroxychloroquine, sulfasalazine) for at least 6 months and on stable dose for at least 3 months with active disease requiring additional therapy.

The eligible study population only partly reflects the indication of MabThera as eligible patients in study RI-01-003 were not allowed prior TNF-alfa therapy and other biologics. With regards to demonstrating similarity between DRL_RI and MabThera/Rituxan, this is acceptable as prior treatment may introduce heterogeneity to the study population. In addition, the 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis recommend that patients with an inadequate response to methotrexate (as required in study RI-01-003) should escalate to a bDMARD (eg. rituximab) or tsDMARD, because of the more rapid onset of benefit. Apart from the deviation of prior therapy, the study population was also overall comparable to that of the historical studies DANCER and REFLEX.

While the primary objective of the study was to demonstrate PK similarity, efficacy parameters were evaluated as secondary endpoints (ACR 20, ACR50 and ACR70, continuous variable DAS-28, change from baseline for HAQ-DI and VAS). For all the secondary endpoints, there was no formal statistical hypothesis put forth, a priori. All efficacy endpoint analyses were performed for the PP and ITT Analysis Set.

Efficacy data and additional analyses

Pivotal efficacy study RI-01-006

162 subjects were randomly assigned to DRL_RI treatment and 155 subjects to MabThera treatment. Baseline demographic and disease characteristics were largely similar between the two treatment groups. The majority of subjects were White (66.6%) with a median age of 58.0 years, had intermediate risk (FLIPI2) category and a low grade tumor (Grade 1-2). Treatment compliance was high with 89.2% of patients receiving all 7 doses. A slightly higher percentage of patients in DRL_RI group (152 subjects - 93.8%) compared to MabThera group (139 subjects - 89.7%) completed the study. There were no significant differences in discontinuation rates between both study groups.

The primary endpoint, BOR up to week 28 based on central radiology review in the ITT population, was 80.25% in the DRL_RI group and 79.35% in the MabThera group. The analysis of BORR showed an estimated difference of 0.89% (DRL_RI minus MabThera), with a 95% CI of (-8.05%, 9.93%), which fell entirely within the pre-specified equivalence margin of ±17%.

Additional analyses based on PPS and investigator assessment as well as all sensitivity analyses (ITT and PPS) have been performed for the primary endpoint, all of which met the equivalence criteria, thus supporting similarity. The differences of BORR for supplementary analyses ranged from -2.68% to 1.39%.

As for the summary of best response, CR rates (ITT analysis) were comparable between the treatment arms with slight numerical differences in the rates of CRu and for DRL_RI and MabThera. The same is noted for the PP analysis, while responses based on investigator assessment are reversed with a slightly higher CR rate but comparable CRu and PR rates. Nevertheless, BOR results are overall supporting similarity of DRL_RI to MabThera.

Subgroup analyses indicated that equivalence of the primary endpoint ORR could be demonstrated over subgroups such as age, gender, Ann Arbor Stage and the stratification factors FLIPI2 index and geographical region. For the third stratification factor, tumor grade, the difference of BORR for Grades 2 and 3a deviated considerably (-19.49% and -9.94%, respectively) with wide confidence intervals ([-38.09, -0.89] and [-33.99, 14.12], respectively) exceeding the lower limit of -17% of the predefined equivalence margin. Of note the point estimate for grade 2 lies outside of the margin and the respective 95% confidence interval suggests a nominally significant difference between the two treatments. With the responses to the D120 LoQ the Applicant provided data from analyses of baseline characteristics and demographics in the specific subgroups of patients with tumor grade 2 and 3a, respectively. There were some imbalances between the treatment groups especially with regards to potential risk factors (eg. or both Grade 2 and 3a a higher proportion of patients in the Mabthera arm had hemoglobin levels <120 g/L compared to DRL_RI). However, overall, there is no distinct combination of risk factors that can be applied to both tumor grade 2 and 3a that would explain the observed differences in BORR especially compared to tumor grade 1.

It is noted, that for patients with tumor grade 1, which accounts for the majority of patients in both arms (DRL_RI N=101/162 (62.3%), Mabthera N=96/155 (61.9%)), DRL_RI seems to be slightly inferior to Mabthera with a difference of 8.19 and an upper 95% CI of [-0,88, 17.26] outside of the predefined margin of +17%. Additional analyses in this regard were conducted to investigate whether these differences were potentially attributed to specific baseline or disease characteristics. BORR up to week 28 varied between the treatment arms among patients with certain baseline and disease characteristics. However, these differences were noted for all tumor grades and not specifically for tumor grade 1 and no clear pattern could be identified. Moreover, CR, CRu, PR and SD were largely comparable in both treatment groups. The same applies for ORR at week 52. Hence, the observed differences in BORR at week 28 in the subgroup of patients with tumor grade 1 compared to tumor grades 2 and 3a seem to reflect individual differences in outcomes rather than clinically relevant differences between DRL_RI and MabThera.

For the secondary endpoint ORR at week 28 based on central review CR, CRu and PD results are slightly in favour of the MabThera arm. It is however noted that the number of missing data is almost three times higher than that of the DRL_RI arm (10.3% vs 3.7%) which might have had an impact on the observed differences in the individual response categories. The difference of missing data at week 28 is also noted for the investigator assessment, however here results favour the DRL_RI arm. Upon request, the Applicant provided supplementary analyses where all missing values and subjects with "unknown" response were treated as either responders or non-responders, respectively. As these analyses are not a conservative approach in a biosimilarity study, the Rapporteur conducted additional analyses by defining missing values as responders in one arm and non-responders in the other. These strictly conservative approaches lead to an estimated risk difference of -9.85% and 95% confidence interval based on (unstratified) Miettinen and Nurminen (MN) method of (-18.59, -1.07) in the one extreme and 8.55% (- 0.60, 17.73) in the other extreme. In both cases the margin of ±17% was not

met. Additional tipping point analyses showed that only slightly less conservative assumptions led to an acceptance of biosimilarity in both cases, which overall is considered reassuring.

With the responses to the D120 LoQ, updated data for DOS, PFS and OS have been provided. A considerable change of the estimated PFS rate at week 28 is noted between the initial submission (0.79 [95% CI: 0.67, 0.91]) and the updated data on D121 (0.99 [95% CI: 0.91 [0.86, 0.95]). It is unclear, whether this is attributed to censoring events at the time of the week 28 analysis or just an error of numbers in the initial submission.

While there are no major differences in the rates of DOR, PFS and OS between the treatment arms, it is noted that for all of these secondary parameters the rates are minimally lower in the DRL_RI arm from week 28 through week 52 compared to the MabThera arm. However, in the context of a comparability exercise, these parameters are not considered to sufficiently sensitive to detect clinically relevant differences.

PET-CT data and consequently assessment by Lugano criteria was available for 49.8% of patients. More patients in the MabThera arm had an assessment of CR while in the DRL_RI arm the number of patients with PR was higher. However, given that data were only available for half of the enrolled population, no meaningful conclusion can be drawn. In addition, when combined as responders (CR + PR), rates were similar between the treatment arms. Concordance between Cheson 1999 and Lugano 2014 criteria was 79.1% with similar concordance rates in both treatment arms.

Supportive study RI-01-003

N=91, N=92 and N=93 subjects were assigned to DRL_RI, Rituxan and MabThera treatment, respectively.

Demographic and baseline characteristics were overall comparable between the treatment arms except for an imbalance of RA parameters (Total Swollen and Tender Joint Counts). Median and Mean values were consistently higher in the DRL_RI group compared to the other treatment arms indicating a higher disease activity at baseline in this group. This is also reflected in the baseline scores of HAD-DI and VAS and finally in the baseline score of mean DAS-28-CRP (since calculation parameters include swollen and tender joints as well as VAS).

As for the change in mean DAS28-CRP, scores decreased from Baseline to Week 24 in all 3 treatment arms not indicating clinically meaningful differences between the groups.

For ACR20 the proportion of patients with response was largely comparable for DR_RI and MabThera through week 24. For ACR50 and ACR 70 responses were initially higher in the MabThera group until week 16 and 12, respectively. However, at week 24 response rates equalised with comparable values for DRL_RI and MabThera.

As noted above, baseline HAQ-DI scores were highest in the DRL_RI arm. Up to week 16 the change from baseline of HAQ-DI for DRL_RI was comparable to that of MabThera. After week 16 a plateau was observed for MabThera while for DRL_RI scores further decreased with final values similar to those of MabThera at week 24. There were also no apparent differences regarding changes from baseline in VAS scores.

Overall, the slightly higher disease activity at baseline in the DRL_RI arm did not result in major differences between the treatment groups regarding the results of the secondary efficacy endpoints.

The Applicant provided an overview of efficacy data from published literature in order to compare the ACR and DAS28CRP data from study RI-01-003 to historical data. Numerical differences in outcome parameters are noted between some of the studies. However, results from the RI-01-003 are largely in accordance and not inferior to those observed in other trials.

Although the study was not powered for comparison of efficacy, the outcomes support the conclusion of similarity in the non-oncology indication Rheumatoid Arthritis.

2.6.7. Conclusions on the clinical efficacy

In the pivotal efficacy study in subjects with LTB-FL, equivalence criteria were met for the primary endpoint, BORR up to week 28. Additional analyses of the primary endpoint as well as secondary endpoints confirm bioequivalence. Updated week 52 data and the final CSR have been provided. Similarity of efficacy can be considered demonstrated.

Although the supportive PK study in patients with RA was not powered for comparison of efficacy, the outcomes support the conclusion of similarity between DRL_RI and MabThera.

2.6.8. Clinical safety

Comparative safety data of the biosimilar product and the European innovator product MabThera were obtained from three clinical trials: one in low-tumour-burden follicular lymphoma (LTB-FL, Study RI-01-006), and two in RA (PK equivalence study RI-01-003 and single transition study RI-01-007).

The safety data from the two RA studies RI-01-003 and RI-01-007 were not pooled because of differences in the study design: the "transition trial" RI-01-007 was performed in patients who had been previously exposed to at least 1 full course of rituximab, whereas study RI-01-003 was done in patients who were treatment-naïve.

The safety analysis period was 52 weeks in studies RI-01-003 and RI-01-006, and 26 weeks in study RI-01-007. Both RA studies are completed.

Overall, 323 patients were exposed to DRL_RI in the clinical development program: 162 LTB-FL patients from study RI-01-006, 91 rituximab-naïve RA patients from study RI-01-003, and 70 rituximab-exposed RA patients from study RI-01-007.

Table 40 Clinical studies relevant to safety

Study Number Start Date/ End Date Report Status	Subject Population Studied	Design Type of Control Blind	Dose(s) and Frequency of Dosing	Treatment Duration (does not include follow-up period)	No. of Subjects Treated
RI-01-003 18 Nov 2014/10 Jun 2017 Complete; Full	Patients with moderate to severe active, seropositive RA with an inadequate response to methotrexate-based therapy	Randomised, multi-centre, double-blind, parallel-group study	DRL_RI/RP/RMP at the dose of 1000 mg on Day 1 and Day 15 as an i.v infusion	2 doses over 15 days	276
RI-01-006 15 May 2019/13 Sep 2022 (Week 28 visit) Completed CSR till Week 28. Study is ongoing.	Male or female patients aged ≥18 years of age Histologically confirmed, Grade 1-3a, previously untreated, CD20-positive, LTB-FL as per GELF criteria	Randomised, multi-centre, double-blind, parallel group study	The study drug DRL_RI or MabThera administered as an i.v infusion, at a dose of 375 mg/m^2 of BSA (induction treatment: 4 i.v infusions weekly; maintenance treatment: 4 i.v infusions 8 weekly; Total of 8 doses)	Patients received induction treatment consisting of weekly i.v infusions up to Week 4 followed by maintenance treatment consisting of i.v infusion every 8 weeks from Week 12 up to Week 36	315

Study Number Start Date/ End Date Report Status	Subject Population Studied	Design Type of Control Blind	Dose(s) and Frequency of Dosing	Treatment Duration (does not include follow-up period)	No. of Subjects Treated
RI-01-007 21 Jan 2020/20 Apr 2022 Complete	Male or female patients aged ≥18 years of age with a diagnosis of active RA who received at least 1 full course (comprising of two 1000-mg infusions) of US or EU-rituximab	Randomised, multi-centre, double-blind, parallel group study	DRL_RI/RP/RMP at the dose of 1000 mg on Day 1 and Day 15 as an i.v infusion	2 doses over 15 days	140

Abbreviations: BSA = body surface area; CD = cluster of differentiation; CSR = clinical study report; DRL_RI = Dr. Reddy's rituximab; EU = European union; GELF = Groupe D'Etude des Lymphomes Folliculaires; i.v = intravenous; LTB-FL = low tumour burden follicular lymphoma; RA = rheumatoid arthritis; RMP = EU-approved- MabThera; RP = US-licensed Rituxan; US = United States.

Source: Study RI-01-003 (Section 5.3.3.2.1), Study RI-01-006 (Section 5.3.5.1.1), Study RI-01-007 (Section 5.3.5.1.2)

In addition, safety data from another clinical trial, namely study RI-01-002 conducted in CD20-positive DLBCL patients with Reditux in India, are presented, to provide transparency with regards to the full set of clinical data available. The applicant states that study RI-01-002 was conducted for supporting approval in emerging market countries and hence is considered as supportive only. Study RI-01-002 underwent multiple changes during execution; furthermore, it has been outlined by the applicant that there are "slight differences" in the manufacturing process between DRL_RI and Reditux. Thus, from the Rapporteur´s point of view, those data are not considered relevant for the current submission.

2.6.8.1. Patient exposure

Table 41 Estimated total exposure from Clinical Studies

Indication	Study	Duration of Exposure	Estimated Number of Subjects Exposed to DRL_RI (N)
LTB-FL	RI-01-006	At least 1 dose	162
		Four weekly doses	162
		Four infusions over 8 weeks (till Week 28 i. e., 4+3 doses)	159
RA	RI-01-003	At least 1 dose	91
		Both doses (Day 1 and Day 15)	90
RA	RI-01-007	At least 1 dose	70
		Both doses (Day 1 and Day 15)	69
Total		At least 1 dose	323

Comparative safety data from the pivotal **Phase 3 LTB-FL study RI-01-006** involved 315 patients in the safety set (DRL_RI: n=162, EU-MabThera n=153). A total of 220 (69.4%) subjects have already completed the study (end of study [EOS] visit); 118 (72.8%) subjects in the DRL_RI group and 102 (65.8%) subjects in the MabThera group.

Overall, baseline characteristics with regard to ECOG PS, serum beta-2 microglobulin, longest diameter of largest involved node for FLIPI2 score, FLIPI2 Score, and histological tumour grade for FL were balanced between treatment arms, and the population that was investigated was sufficiently sensitive for the evaluation of similarity from a safety (and efficacy) perspective.

The mean (SD) time since histological confirmation of FL was comparable between the treatment arms: 5.20 (8.458) months in the DRL_RI and 4.78 (8.524) months in the MabThera arm.

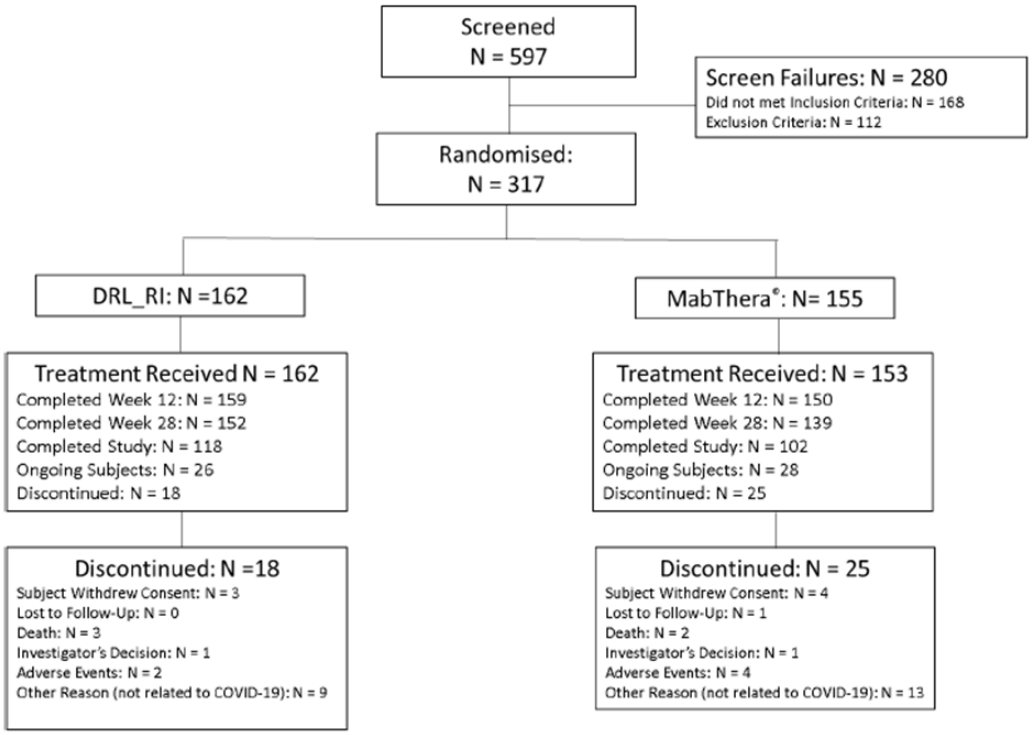
In study RI-01-006, DRL_RI or MabThera was administered as iv infusion, at a dose of 375 mg/m^2 of body surface area. There was an induction treatment period, during which four weekly iv infusions

were administered, followed by a maintenance treatment period, during which further four iv infusions were administered every 8 weeks (i.e., Wk 12, Wk 20, Wk 28, Wk 36).

A total of 597 subjects were screened, of whom 317 subjects were randomised 1:1 into either the DRL_RI treatment arm (n=162) or the MabThera treatment arm (n=155).

Of the 315 subjects in the safety data set, 274 (87.0%) subjects initiated and were included in the safety follow-up up to Week 28: 142 (87.7%) subjects in the DRL_RI group and 132 (86.3%) subjects in the MabThera group. This was because two subjects in the MabThera arm were randomised, but not dosed.

Figure 16 Subject disposition by treatment in RI-01-006 (All screened subjects)



Abbreviations: DRL_RI = Dr. Reddy's rituximab; COVID-19 = coronavirus disease of 2019; N = number of subjects in the screened Analysis Set for the overall study group.

Overall, single dose of study drug was missed in 8 (2.5%) subjects; 2 (1.2%) subjects in the DRL_RI group and 6 (3.9%) subjects in the MabThera group. More than 14 days dose delay was reported in 28 (8.9%) subjects; 11 (6.8%) subjects in the DRL_RI group and 17 (11.1%) subjects in the MabThera group.

Treatment compliance up to Week 28 was 100% in both treatment arms. The median duration of treatment was 27.10 weeks (range: 0.1 weeks to 38.1 weeks).

The actual dose for a specific subject was calculated based upon his/her BSA. The mean cumulative actual dose received was comparable between the treatment arms up to Week 28.

There were few dose interruptions reported during the study. Major reasons for dose interruptions were AEs in 46 (14.6%) subjects; 21 (13.0%) subjects in the DRL_RI group and 25 (16.3%) subjects in the MabThera group. Dose interruption due to other reasons were reported in 2 (1.3%) subjects in the MabThera group, only. No treatment discontinuation was reported during the study.

In the **PK equivalence study RI-01-003**, 276 patients with moderate to severe active, seropositive RA with an inadequate response to methotrexate-based therapy were included. They received 2 doses

of 1000 mg of DRL_RI (n=91), US-Rituxan (n=92) or EU-MabThera (n=93) over 15 days (on D1 and D15).

Demographic and baseline disease characteristics were overall comparable between the three treatment arms.

Of the 276 patients randomised, 254 patients completed and 22 patients discontinued during Part 1 (Baseline to Week 24). A total of 240 (87.0%) patients (DRL_RI: 82 [90.1%], Rituxan: 79 [85.9%], MabThera 79 [84.9%]) completed Week 52 visit.

Another 14 (5.1%) patients discontinued prior to Week 52 (post week 24 completion); the primary reasons for discontinuation were AE and withdrawal of consent.

In the DRL_RI arm, 91 patients received at least 1 dose, and 90 patients received both doses of IMP.

In the Rituxan group, 92 patients received the Rituxan infusion on Day 1, and 88 patients received the infusion on Day 15.

In the MabThera group, 93 patients received the MabThera infusion on Day 1 and 86 patients received the infusion on Day 15.

In the **Phase 3 transition trial RI-01-007** set up to comply with US-FDA requirements, 140 patients with a diagnosis of active RA who had completed at least 1 full course of US -Rituxan or EU-MabThera (consisting of two 1000 mg rituximab infusions on D1 and 8) were randomized to receive either 1 treatment course (2 doses over 15 days) of DRL_RI (n=70) or to stay on their prior therapy with the respective Rituxan or MabThera (n=70).

Demographic and baseline disease characteristics were overall comparable between the treatment arms.

Of the 140 randomized subjects, a total of 134 (95.7%) subjects completed the Week 12 visit, 138 (98.6%) subjects completed study treatment, and 2 (2.9%) subjects in the DRL_RI group discontinued study treatment due to an AE (1 subject) and withdrawal (1 subject). One subject discontinued from the study following withdrawal of consent at Week 8 but received both rituximab doses; however, the investigator documented this as "subject discontinued from study treatment".

Five (3.6%) subjects did not complete the study: 3 (4.3%) subjects from the DRL_RI group and 2 (2.9%) subjects from the Rituxan or MabThera groups. The reasons for study termination were as follows: subject chose to withdraw from the study (2 subjects in the DRL_RI group), lost to follow-up (1 subject in each treatment group) and other reason (1 subject in the Rituxan or MabThera groups due to subject safety and institution restriction for COVID-19).

The clinical study protocol was amended to increase the duration of follow-up from 12 to 26 weeks during the study conduct. Subjects were re-consented for a longer safety follow-up to 26 weeks. A total of 118 subjects re-consented for the Week 26 follow-up visit (59 in each treatment group), of which 116 (98.3%) subjects completed (57 [96.6%] subjects from DRL_RI and 59 [100%] subjects from Rituxan or MabThera groups). Two (1.7%) subjects from the DRL_RI discontinued prior to the Week 26 visit due to AEs (COVID-19 and COVID-19 pneumonia).

2.6.8.2. Adverse events

In the **Phase 3 LTB-FL study RI-01-006**, a total of 530 AE occurred in 197 subjects (62.5%), with 248 events in 100 subjects in the DRL_RI group (61.7%) and 282 events in 97 subjects in the MabThera group (63.4%). The incidence and severity of the reported TEAE was generally comparable between the treatment arms, with 235 events in 95 subjects (58.6%) in the DRL_RI arm and 260

events in 93 subjects (60.8%) in the MabThera arm. TEAE were mainly mild (298 events in 137 subjects) or moderate (149 events in 87 subjects) by severity. There were no distinct differences observed between treatment arms.

Table 42 Overview of Adverse events in RI-01-006 (Safety population)

Category	DRL_RI (N=162) n (%) E	MabThera (N=153) n (%) E	Overall (N=315) n (%) E
No. of Adverse events	100 (61.7) 248	97 (63.4) 282	197 (62.5) 530
TEAEs	95 (58.6) 235	93 (60.8) 260	188 (59.7) 495
Non-TEAEs	13 (8.0) 13	18 (11.8) 22	31 (9.8) 35
Infusion-related AEs	28 (17.3) 45	32 (20.9) 49	60 (19.0) 94
Severity (CTCAE Grade)[1]			
Grade 1: Mild	70 (43.2) 137	67 (43.8) 161	137 (43.5) 298
Grade 2: Moderate	37 (22.8) 66	50 (32.7) 83	87 (27.6) 149
Grade 3: Severe or medically significant	16 (9.9) 27	9 (5.9) 11	25 (7.9) 38
Grade 4: Life-threatening or disabling	4 (2.5) 4	5 (3.3) 5	9 (2.9) 9
Grade 5: Death related to AE	1 (0.6) 1	0	1 (0.3) 1
TEAE ≥ CTCAE Grade 3	20 (12.3) 32	13 (8.5) 16	33 (10.5) 48
Serious TEAEs	13 (8.0) 16	13 (8.5) 14	26 (8.3) 30
Non-serious TEAEs	94 (58.0) 219	92 (60.1) 246	186 (59.0) 465
TEAEs related to study drug	45 (27.8) 81	47 (30.7) 80	92 (29.2) 161
Action taken with study drug for TEAEs[1]			
Drug withdrawn	1 (0.6) 1	2 (1.3) 2	3 (1.0) 3
Drug interruption[2]	26 (16.0) 31	32 (20.9) 51	58 (18.4) 82
Dose not changed	82 (50.6) 193	80 (52.3) 198	162 (51.4) 391
Not Applicable	6 (3.7) 10	5 (3.3) 9	11 (3.5) 19
TEAEs outcome [1]			
Not Recovered/Not Resolved	36 (22.2) 52	28 (18.3) 42	64 (20.3) 94
Recovered/Resolved	77 (47.5) 176	89 (58.2) 208	166 (52.7) 384
Recovered/Resolved with Sequelae	1 (0.6) 1	0	1 (0.3) 1
Recovering/Resolving	5 (3.1) 5	6 (3.9) 10	11 (3.5) 15
Fatal	1 (0.6) 1	0	1 (0.3) 1
TEAEs related to medication error	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DRL_RI = Dr. Reddy's rituximab; E = Number of events; MedDRA = Medical Dictionary for Regulatory Activities n = The number of subjects in specific category; N = The number of subjects in the Safety Analysis Set; TEAE = treatment-emergent adverse event.
%: calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100).
All AEs were coded using MedDRA version 25.0. TEAEs include any AEs occurring or worsening after the first dose of study medication.

The most frequently reported TEAE were in the SOC of infections and infestations (overall, 25 TEAEs in 24 [7.6%] subjects) followed by skin and subcutaneous tissue disorders (overall, 23 [6.3%] TEAEs in 20 subjects). The most frequently reported TEAE by Preferred Terms were COVID-19 infections (overall, 25 TEAEs in 24 [7.6%] subjects) followed by pruritus (overall, 23 TEAEs in 20 [6.3%] subjects). No imbalances regarding TEAE types/ categories were observed between biosimilar and RMP.

Table 43 Treatment emergent AEs with incidence ≥ 5% by SOC and PT in RI-01-006 Safety population

System Organ Class Preferred Term	DRL_RI (N=162) n (%) E	MabThera (N=153) n (%) E	Overall (N=315) n (%) E
No. of subjects with at least one TEAE	25 (15.4) 31	39 (25.5) 43	64 (20.3) 74
Gastrointestinal disorders	5 (3.1) 6	10 (6.5) 11	15 (4.8) 17
Nausea	5 (3.1) 6	10 (6.5) 11	15 (4.8) 17
General disorders and administration site conditions	1 (0.6) 1	8 (5.2) 8	9 (2.9) 9
Pyrexia	1 (0.6) 1	8 (5.2) 8	9 (2.9) 9
Infections and infestations	10 (6.2) 10	14 (9.2) 15	24 (7.6) 25
COVID-19	10 (6.2) 10	14 (9.2) 15	24 (7.6) 25
Skin and subcutaneous tissue disorders	11 (6.8) 14	9 (5.9) 9	20 (6.3) 23
Pruritus	11 (6.8) 14	9 (5.9) 9	20 (6.3) 23

Abbreviations: COVID-19 = coronavirus disease 2019; DRL_RI = Dr. Reddy's rituximab; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
n = number of subjects reporting at least one adverse event in each category; N = number of subjects in the Safety Analysis Set; E = number of events.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100).
All adverse events were coded using MedDRA version 25.0.
Treatment-emergent adverse events included any AEs occurring or worsening on or after the first dose of study medication.

Numbers of TEAE judged related to study drug were comparable between both treatment arms (DRL_RI: 81 events in 45 subjects [27.8%], MabThera: 80 events in 47 subjects [30.7%]).

The incidence of infusion related AEs was comparable between treatment arms: they were reported in 28 patients (17.3%) in the DRL_RI arm and in 32 patients (20.9%) in the MabThera arm.

For the **PK equivalence study RI-01-003**, safety data are reported separately for Part 1 (until Week 24) and for Part 2 (from Wk 24 until Wk 52).

During Part 1, comparable numbers of subjects experienced at least one TEAE: 33 subjects (36.3%) in the DRL_RI arm, 30 subjects (32.6%) in the Rituxan arm, and 37 subjects (39.8%) in the MabThera arm. The numbers of TEAE as well as of TEAE judged related to study drug were overall comparable between study arms, with a higher incidence of related TEAE in the MabThera arm.

Table 44 Overview of Treatment emergent events in study RI-01-003 (Safety Population)

	DRL_RI (N=91)	Rituxan (N=92)	MabThera (N=93)
Part 1*			
Total number of TEAEs, n	71	67	76
Patients with at least one TEAE, n (%)	33 (36.3)	30 (32.6)	37 (39.8)
Total number of related TEAE, n	12	15	23
Patients with at least one treatment related TEAE, n (%)	10 (11.0)	10 (10.9)	12 (12.9)
Study discontinuation due to AE, n (%)	1 (1.1)	3 (3.3)	6 (6.5)
Total number of SAEs, n	2	5	8
Total number of related SAE, n	1	3	4
Patients with at least one SAE, n (%)	2 (2.2)	4 (4.3)	6 (6.5)
Patients with at least one treatment related SAE, n (%)	1 (1.1)	3 (3.3)	4 (4.3)
Part 2**			
Total number of TEAEs, n	42	40	51
Patients with at least one TEAE, n (%)	27 (29.7)	28 (30.4)	29 (31.2)
Total number of related TEAE, n	8	10	14
Patients with at least one treatment related TEAE, n (%)	8 (8.8)	9 (9.8)	12 (12.9)
Study discontinuation due to AE, n (%)	1 (1.1)	1 (1.1)	0
Total number of SAEs, n	1	1	4
Total number of related SAE, n	0	0	3
Patients with at least one SAE, n (%)	1 (1.1)	1 (1.1)	4 (4.3)
Patients with at least one treatment related SAE, n (%)	0	0	3 (3.2)

Abbreviations: AE = adverse event; DRL_RI = Dr. Reddy's rituximab; N = number of patients in the Safety Population; n = number of subjects in a specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
*Data for Part 1 are considered from the first dose until Week 24.
**Part 2 covers AEs either ongoing at the end of Part 1 or reported after Week 24.

The most commonly reported TEAEs related to study drug were infusion related reactions (overall 4 events in 4 [1.4%] patients: DRL_RI: 1 event in 1 [1.1%] patient, Rituxan: 2 events in 2 [2.2%] patients, MabThera: 1 event in 1 [1.1%] patient).

Majority of the TEAE reported in the study were mild in severity (DRL_RI: 63 of 71 events in 25 [27.5%] patients, Rituxan: 55 of 67 events in 24 [26.1%] patients, MabThera: 60 of 67 events in 25 [26.9%] patients). Few TEAE were classified as severe. Their incidences were comparable between the treatment arms: 2 (2.2%) patients in the DRL_RI arm (sudden death, pneumonia), 3 (3.3%) patients in the Rituxan arm (febrile neutropenia, neutropenia, humerus fracture, infusion-related reaction), and 4 (4.3%) patients in the MabThera arm (pyrexia, H1N1 influenza, atrial fibrillation, cardio-respiratory arrest, femoral neck fracture, forearm fracture) experienced severe TEAE. All severe TEAEs resolved within 24 weeks except for 1 patient in the DRL_RI arm: sudden death) with a fatal outcome.

During Part 1 of the study, the most frequently reported TEAE by PT were upper respiratory tract infection (SOC Infections and infestations; 12 [4.3%] patients), cough (SOC Respiratory, thoracic and mediastinal disorders; 9 [3.3%] patients), and pyrexia (SOC General disorders; 9 [3.3%] patients) with no distinct imbalances between treatment groups.

Table 45 **Treatment emergent events occurring in > 2% of subjects in any treatment group by PT**

Study RI-01-003 at Week 24 (Safety Population)

System Organ Class Preferred Term	DRL_RI N=91 n (%) nAE	Rituxan (N=92) n (%) nAE	MabThera (N=93) n (%) nAE	Total (N=276) n (%) nAE
Number of patients with at least 1 TEAE	33 (36.3) 71	30 (32.6) 67	37 (39.8) 76	100 (36.2) 214
Infections and infestations	15 (16.5) 17	9 (9.8) 10	15 (16.1) 17	39 (14.1) 44
Upper respiratory tract infection	4 (4.4) 4	3 (3.3) 3	5 (5.4) 5	12 (4.3) 12
Nasopharyngitis	2 (2.2) 2	4 (4.3) 5	1 (1.1) 1	7 (2.5) 8
Urinary tract infection	2 (2.2) 2	2 (2.2) 2	2 (2.2) 2	6 (2.2) 6
Gastrointestinal disorders	7 (7.7) 10	5 (5.4) 9	6 (6.5) 6	18 (6.5) 25
Nausea	1 (1.1) 1	2 (2.2) 2	1 (1.1) 1	4 (1.4) 4
Mouth ulceration	2 (2.2) 2	1 (1.1) 1	0	3 (1.1) 3
Abdominal pain upper	2 (2.2) 2	0	0	2 (0.7) 2
Investigations	5 (5.5) 6	6 (6.5) 8	6 (6.5) 6	17 (6.2) 20
Alanine aminotransferase increased	1 (1.1) 1	2 (2.2) 2	1 (1.1) 1	4 (1.4) 4
Aspartate aminotransferase	0	2 (2.2) 2	0	2 (0.7) 2
Musculoskeletal and connective tissue disorders	6 (6.6) 9	4 (4.3) 4	6 (6.5) 6	16 (5.8) 19
Rheumatoid arthritis	3 (3.3) 5	1 (1.1) 1	2 (2.2) 2	6 (2.2) 8
Back pain	0	0	2 (2.2) 2	2 (0.7) 2
General disorders and administration site conditions	5 (5.5) 6	6 (6.5) 6	4 (4.3) 4	15 (5.4) 16
Pyrexia	2 (2.2) 2	4 (4.3) 4	3 (3.2) 3	9 (3.3) 9
Respiratory, thoracic and mediastinal disorders	3 (3.3) 3	6 (6.5) 7	6 (6.5) 7	15 (5.4) 17
Cough	3 (3.3) 3	3 (3.3) 3	3 (3.2) 3	9 (3.3) 9
Throat irritation	0	2 (2.2) 2	1 (1.1) 2	3 (1.1) 4
Blood and lymphatic system disorders	2 (2.2) 4	8 (8.7) 11	4 (4.3) 6	14 (5.1) 21
Anaemia	1 (1.1) 1	5 (5.4) 5	1 (1.1) 1	7 (2.5) 7
Neutropenia	1 (1.1) 1	2 (2.2) 2	1 (1.1) 1	4 (1.4) 4
Eosinophilia	0	1 (1.1) 1	2 (2.2) 2	3 (1.1) 3
Skin and subcutaneous tissue disorders	3 (3.3) 4	3 (3.3) 5	5 (5.4) 6	11 (4.0) 15
Pruritus	0	2 (2.2) 3	1 (1.1) 1	3 (1.1) 4
Rash	0	1 (1.1) 1	2 (2.2) 2	3 (1.1) 3
Injury, poisoning and procedural complications	2 (2.2) 2	4 (4.3) 4	2 (2.2) 3	8(2.9) 9
Infusion-related reaction	1 (1.1) 1	2 (2.2) 2	1 (1.1) 1	4 (1.4) 4
Vascular disorders	1 (1.1) 1	0	3 (3.2) 3	4 (1.4) 4
Hypertension	1 (1.1) 1	0	2 (2.2) 2	3 (1.1) 3

Abbreviations: DRL_RI = Dr. Reddy's rituximab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients within each treatment group under Safety Population; n = total number of patients meeting the event; nAE = number of adverse events; TEAE = treatment-emergent adverse event.
Adverse event (AE) terms were coded by system organ class (SOC) and Preferred Term using MedDRA version 19.1.
Patients experiencing multiple events within the same SOC or Preferred Term were counted only once under those categories. Percentages were based on number of patients within each treatment group under Safety Population (N).
Ongoing AEs during Part 1 are also presented.

Incidences of TEAE were also comparable between treatment arms during Part 2 of the study. Few treatment-related TEAE were reported (8 events in 8 subjects in the DRL_RI arm, 10 events in 9 subjects in the Rituxan arm and 14 events in 12 subjects in the MabThera arm).

The majority of the TEAE reported ongoing at the end of Part 1 or reported in Part 2 of the study were considered as mild in severity (DRL_RI: 35 events in 20 [22.0%] patients, Rituxan: 35 events in 24 [26.1%] patients, MabThera: 46 events in 24 [25.8%] patients). Severe TEAE were reported in 1

(1.1%) patient in DRL_RI, 1 (1.1%) patient in Rituxan, and 3 (3.2%) patients in MabThera. All severe TEAE post Week 24 resolved during the study except for 1 event in 1 patient in the DRL_RI arm: sudden death) with fatal outcome.

The most frequently reported TEAE by PT after Week 24 were evenly distributed across the treatment groups: B lymphocyte count decreased (SOC Investigations; 20 events in 20 [7.2%] patients), rheumatoid arthritis (SOC Musculoskeletal and connective tissue disorders; 9 events in 8 [2.9%] patients), upper respiratory tract infection (SOC Infections and infestations; 6 events in 5 [1.8%] patients), cough (SOC Respiratory, thoracic and mediastinal disorders; 6 events in 6 [2.2%] patients), and pyrexia (SOC General disorders; 6 events in 6 [2.2%] patients).

Table 46 Treatment emergent events occurring in > 2% of subjects in any treatment group by PT

Study RI-01-003 Week 52 (Post Week 24) (Safety Population)

System Organ Class Preferred Term	DRL_RI N=91 n (%) nAE	Rituxan (N=92) n (%) nAE	MabThera (N=93) n (%) nAE	Total (N=276) n (%) nAE
Number of patients with at least 1 TEAE	27 (29.7) 42	28 (30.4) 40	29 (31.2) 51	84 (30.4) 133
Investigations	8 (8.8) 8	10 (10.9) 12	10 (10.8) 11	28 (10.1) 31
B lymphocyte count decreased	7 (7.7) 7	5 (5.4) 5	8 (8.6) 8	20 (7.2) 20
Alanine aminotransferase increased	0	2 (2.2) 2	1 (1.1) 1	3 (1.1) 3
Aspartate aminotransferase	0	2 (2.2) 2	1 (1.1) 1	3 (1.1) 3
Infections and infestations	4 (4.4) 6	8 (8.7) 9	7 (7.5) 12	19 (6.9) 27
Upper respiratory tract infection	1 (1.1) 1	3 (3.3) 3	1 (1.1) 2	5 (1.8) 6
Body tinea	1 (1.1) 1	0	2 (2.2) 2	3 (1.1) 3
Musculoskeletal and connective tissue disorders	6 (6.6) 7	5 (5.4) 5	7 (7.5) 8	18 (6.5) 20
Rheumatoid arthritis	3 (3.3) 3	1 (1.1) 1	4 (4.3) 5	8 (2.9) 9
Gastrointestinal disorders	4 (4.4) 5	4 (4.3) 4	1 (1.1) 3	9 (3.3) 12
Mouth ulceration	2 (2.2) 2	0	1 (1.1) 3	3 (1.1) 5
Respiratory, thoracic and mediastinal disorders	1 (1.1) 1	3 (3.3) 3	5 (5.4) 5	9 (3.3) 9
Cough	0	2 (2.2) 2	4 (4.3) 4	6 (2.2) 6
General disorders and administration site conditions	5 (5.5) 5	1 (1.1) 1	2 (2.2) 2	8 (2.9) 8
Pyrexia	3 (3.3) 3	1 (1.1) 1	2 (2.2) 2	6 (2.2) 6
Blood and lymphatic system disorders	1 (1.1) 1	2 (2.2) 2	4 (4.3) 4	7 (2.5) 7
Anaemia	0	2 (2.2) 2	1 (1.1) 1	3 (1.1) 3
Vascular disorders	1 (1.1) 1	0	2 (2.2) 2	3 (1.1) 3
Hypertension	1 (1.1) 1	0	2 (2.2) 2	3 (1.1) 3

Abbreviations: DRL_RI = Dr. Reddy's rituximab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients within each treatment group under Safety Population; n = total number of patients meeting the event; nAE = number of adverse events; TEAE = treatment-emergent adverse event.

Adverse event (AE) terms were coded by system organ class (SOC) and Preferred Term using MedDRA version 19.1.

Patients experiencing multiple events within the same SOC or Preferred Term were counted only once under those categories. Percentages were based on number of patients within each treatment group under Safety Population (N).

Ongoing AEs during Part 1 are also presented.

Data for Part 2 are considered. Post Week 24 visits are considered as Part 2.

In the **single transition trial RI-01-007** in RA patients who had been treated with either MabThera or Rituxan before, TEAE were reported in 24 patients (34.3%; 35 events) in the DRL_RI arm and in 27 patients (38.6%; 54 events) in the MabThera/Rituxan arm. Only few TEAE were of Grade 3 or higher (5 events in 4 subjects in the DRL_RI arm vs. 5 events in 2 subjects in the MabThera/Rituxan arm).

Only 3 events in 3 subjects in the DRL_RI arm and 7 events in 4 subjects in the MabThera/Rituxan arm were considered treatment-related.

Table 47 Overall Summary of Treatment emergent events in Study RI-01-007 (Safety population)

	DRL_RI (N=70)		US-rituximab or EU-rituximab (N=70)	
	Number of events	Number (%) of patients	Number of events	Number (%) of patients
TEAE	35	24 (34.3)	54	27 (38.6)
TEAE of Grade 3 or higher	5	4 (5.7)	5	2 (2.9)
Drug-related TEAE	3	3 (4.3)	7	4 (5.7)
TEAE leading to treatment discontinuation	1	1 (1.4)	1	1 (1.4)
TEAE leading to death	1	1 (1.4)	0	0
Serious TEAE	4	4 (5.7)	5	2 (2.9)
Drug-related serious TEAE	0	0	1	1 (1.4)

Abbreviations: DRL_RI = Dr. Reddy's rituximab; EU-rituximab = European Union approved rituximab (MabThera); N = total number of patients; TEAE = treatment-emergent adverse event; US-rituximab = United States licensed rituximab (Rituxan).

The most commonly reported (>3% of subjects overall) TEAE were attributed to the SOCs Infections and infestations (13.6% of subjects), Gastrointestinal disorders (6.4% of subjects), Nervous system disorders (5.0% of subjects), and Musculoskeletal and connective tissue disorders (3.6% of subjects). Treatment-emergent AEs were more commonly reported in the Rituxan or MabThera group than in the DRL_RI group with regard to these SOCs of Infections and infestations (18.6% of subjects vs. 8.6% of subjects), Gastrointestinal disorders (8.6% of subjects vs. 4.3% of subjects), Nervous system disorders (8.6% of subjects vs. 1.4% of subjects), and Musculoskeletal and connective tissue disorders (4.3% of subjects vs. 2.9% of subjects, respectively).

The most common TEAE by PT reported (>3% of subjects) in the Rituxan or MabThera group included diarrhoea and headache (7.1% of subjects, each) and COVID-19 and nasopharyngitis (4.3% of subjects, each). No AE by PT was reported in more than 3% of subjects in the DRL_RI group.

Table 48 Treatment emergent events occurring in > 3% of subjects in any treatment group by SOC and PT in RI-01-007 (Safety population)

System Organ Class Preferred Term	DRL_RI (N=70) n (%) (e)	US-rituximab or EU-rituximab (N=70) n (%) (e)	Total (N=140) n (%) (e)
Number of subjects with at least 1 TEAE	24 (34.3) (35)	27 (38.6) (54)	51 (36.4) (89)
Infections and infestations	6 (8.6) (7)	13 (18.6) (19)	19 (13.6) (26)
COVID-19	1 (1.4) (1)	3 (4.3) (3)	4 (2.9) (4)
Nasopharyngitis	0	3 (4.3) (3)	3 (2.1) (3)
Gastrointestinal disorders	3 (4.3) (3)	6 (8.6) (9)	9 (6.4) (12)
Diarrhoea	2 (2.9) (2)	5 (7.1) (6)	7 (5.0) (8)
Nervous system disorders	1 (1.4) (1)	6 (8.6) (8)	7 (5.0) (9)
Headache	0	5 (7.1) (5)	5 (3.6) (5)

Abbreviations: COVID-19 = coronavirus disease 2019; DRL_RI = Dr. Reddy's rituximab; EU-rituximab = European Union approved rituximab (MabThera); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the Safety Analysis Set; TEAE = treatment-emergent adverse event; US-rituximab = United States licensed rituximab (Rituxan).

Note: The number of subjects was represented by n. Each subject was counted only once if the subject reported 1 or more events, the number of events is represented as (e) and could include multiple events for a subject. Percentages were based on the number of subjects in the Safety Population. At each level of subject's summarisation, a subject was counted only once if the subject reported 1 or more events.

A TEAE was defined as any adverse event with an onset date on or after the date of the first dose of study drug or began before the first dose of study drug and worsened in severity on or after the first dose of study drug.

Adverse events were coded using MedDRA, Version 25.0.

2.6.8.3. Serious adverse events, deaths, and other significant events

Phase 3 LTB-FL study RI-01-006

A total of 30 treatment-emergent SAEs were reported in 26 subjects (8.3%) during the study. There were no imbalances in SAE incidence between treatment arms (DRL_RI: 16 events in 13 patients; MabThera: 14 events in 13 patients).

The most frequently reported SAE were in the SOC of Infections and infestations. Overall, 18 events were reported in 17 (5.4%) subjects; 11 events in 10 (6.2%) subjects occurred in the DRL_RI group compared to 7 events in 7 (4.6%) subjects in the MabThera group.

The most frequently reported SAE by PT was COVID-19 pneumonia. Overall, 9 events were reported in 9 (2.9%) subjects; 6 events in 6 (3.7%) subjects occurred in the DRL_RI group and 3 events in 3 (2.0%) subjects occurred in the MabThera group.

Table 49 Summary of serious Treatment emergent events reported by SOC and PT in RI-01-006 (Safety population)

System Organ Class Preferred Term	DRL_RI (N=162) n (%) E	MabThera (N=153) n (%) E	Overall (N=315) n (%) E
No. of subjects with at least one SAE	13 (8.0) 16	13 (8.5) 14	26 (8.3) 30
Blood and lymphatic system disorders	1 (0.6) 1	0	1 (0.3) 1
Neutropenia	1 (0.6) 1	0	1 (0.3) 1
Gastrointestinal disorders	0	1 (0.7) 1	1 (0.3) 1
Ileus	0	1 (0.7) 1	1 (0.3) 1
Hepatobiliary disorders	0	1 (0.7) 2	1 (0.3) 2
Cholecystitis acute	0	1 (0.7) 2	1 (0.3) 2
Infections and infestations	10 (6.2) 11	7 (4.6) 7	17 (5.4) 18
COVID-19 pneumonia	6 (3.7) 6	3 (2.0) 3	9 (2.9) 9
Anal abscess	1 (0.6) 1	1 (0.7) 1	2 (0.6) 2
COVID-19	1 (0.6) 1	2 (1.3) 2	3 (1.0) 3
Infection	0	1 (0.7) 1	1 (0.3) 1
Influenza	1 (0.6) 1	0	1 (0.3) 1
Otitis externa	1 (0.6) 2	0	1 (0.3) 2
Injury, poisoning and procedural complications	1 (0.6) 1	0	1 (0.3) 1
Infusion-related reaction	1 (0.6) 1	0	1 (0.3) 1
Musculoskeletal and connective tissue disorders	0	1 (0.7) 1	1 (0.3) 1
Muscular weakness	0	1 (0.7) 1	1 (0.3) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.7) 1	1 (0.3) 1
Squamous cell carcinoma	0	1 (0.7) 1	1 (0.3) 1
Nervous system disorders	2 (1.2) 2	2 (1.3) 2	4 (1.3) 4
Facial paralysis	1 (0.6) 1	0	1 (0.3) 1
Psychomotor hyperactivity	0	1 (0.7) 1	1 (0.3) 1
Syncope	1 (0.6) 1	0	1 (0.3) 1
Transient ischaemic attack	0	1 (0.7) 1	1 (0.3) 1
Respiratory, thoracic and mediastinal disorders	1 (0.6) 1	0	1 (0.3) 1
Chronic obstructive pulmonary disease	1 (0.6) 1	0	1 (0.3) 1

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; DRL_RI = Dr. Reddy's rituximab; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event
n = number of subjects reporting at least one AE in each category = N: number of subjects in the Safety Analysis Set; E = number of events.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100).
All adverse events were coded using MedDRA version 25.0.

Five study drug-related SAE were reported in 5 (1.6%) subjects; 2 events in 2 (1.2%) subjects in the DRL_RI group and 3 events in 3 (2.0%) subjects in the MabThera group. In the DRL_RI group, the study drug-related SAE by PT were IRR and neutropenia (1 event reported in 1 subject, each). In the MabThera group, the study drug-related SAE by PT were anal abscess, muscular weakness, and psychomotor hyperactivity (1 event reported in 1 subject, each). Study drug administration was interrupted due to IRRs and muscular weakness. Study drug dosing was, however, not changed for anal abscess and neutropenia. Study drug was withdrawn in the patient who experienced psychomotor hyperactivity. All SAE were recovered/resolved, except for the SAE of psychomotor hyperactivity.

Table 50 Summary of serious Treatment emergent adverse events by outcome, action taken and PT in RI-01-007 (Safety Analysis Set)

Subject ID (Age/Sex)	Induction Treatment Period	Preferred Term	Severity (CTCAE Grade)	Action Taken with Study Drug	Outcome
[redacted]	DRL_RI	Infusion-related reaction	3	Drug interruption	Recovered/ Resolved
	DRL_RI	Neutropenia	4	Dose not changed	Recovered/ Resolved
	MabThera®	Anal abscess	3	Dose not changed	Recovered/ Resolved
	MabThera®	Muscular weakness	4	Drug interruption	Recovered/ Resolved
	MabThera®	Psychomotor hyperactivity	3	Drug withdrawn	Not Recovered/ Not Resolved

Source: Listing 16.2.4.1 and Listing 16.2.7.4
Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; DRL_RI = proposed rituximab biosimilar; Grade 3 = Severe or medically significant; Grade 4 = Life-threatening or disabling; ID = identification; M = male; F = female
Note: The drug interruption was reported by the investigator in eCRF, it is not derived programmatically. This drug interruption reported by investigator also includes dose delays due to AE.

Overall, 5 deaths were reported in this study, 3 in the DRL_RI arm (1 COVID-19 pneumonia, 2 COVID-19 infections leading to death; and 2 in the MabThera arm (1 COVID-19 pneumonia, 1 pneumonitis).

None of the fatal cases was judged related to study treatment.

One death was reported until the Week 28 cut-off date for primary analysis:

- On 23 Mar 2020, one subject in the DRL_RI group experienced a serious TEAE of COVID-19 pneumonia and died on 26 Mar 2020 due to this event. This death occurred "on treatment", i.e. before Week 36. An autopsy was not performed, and the Investigator considered this event not related to the study drug.

The other 4 deaths occurred before database lock, however were not reported in the primary analysis.

- One subject in the DRL_RI group died on 04 Nov 2021 (Day 345) due to COVID-19 infection. This death occurred "post treatment", i.e. after Week 36. An autopsy was not performed, and the Investigator judged this event not related to the study drug. The subject's age and underlying medical condition were considered as risk factors, which might have contributed to the event.

- One subject in the DRL_RI group experienced an SAE and AESI of COVID-19 leading to death on 19 Dec 2021 (Day 207). This death occurred "on treatment", i.e. before Week 36. An autopsy was not performed, and the Investigator considered this event not related to the study drug.

- One subject in the MabThera group complained of cough and underwent polymerase chain reaction test which turned out to be positive on 18 Sep 2021 (Day 313). The subject died on 01 Oct 2021 (Day 326) due to COVID-19 pneumonia. The subject had diffuse pneumonia in her lungs. This death

occurred "post treatment", i.e. after Week 36. An autopsy was not performed, and the Investigator considered this event not related to the study drug.

- One subject in the MabThera group was diagnosed with community-acquired left sided lower lobe pneumonitis on 23 Nov 2020 (Day 312). The subject died on 05 Dec 2020 (Day 324). This death occurred "post treatment", i.e. after Week 36. An autopsy was not performed, and the Investigator considered this event not related to the study drug.

Table 51 Summary of deaths during study RI-01-006 (Safety population)

System Organ Class Preferred Term	DRL RI (N=162) n (%)	MabThera (N=153) n (%)	Overall (N=315) n (%)
Total number of deaths	3 (1.9)	2 (1.3)	5 (1.6)
Primary cause of death			
Adverse event	3 (1.9)	2 (1.3)	5 (1.6)

Abbreviations: DRL_RI = Dr. Reddy's rituximab; n = number of subjects in each category; N = The number of subjects in the Safety Analysis Set.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100).

With regard to AESI, a total of 94 IRR were reported in 60 (19.0%) subjects during the study. The incidence of infusion-related AE was comparable between treatment arms: they were reported in 28 patients (17.3%) in the DRL_RI arm and in 32 patients (20.9%) in the MabThera arm. The most frequently reported IRR by PT was pruritus (11 events in 8 subjects [4.9%] in the DRL_RI arm; 7 events in 7 subjects [4.6%] in the MabThera arm) followed by throat irritation (7 events in 7 subjects [4.3%] in the DRL_RI arm; 4 events in 4 subjects [2.6%] in the MabThera arm).

PK equivalence study RI-01-003

During Part 1 of the study, 15 SAE were reported in 12 (4.3%) patients (DRL_RI group: 2 [2.2%], Rituxan group: 4 [4.3%], MabThera group: 6 [6.5%]). No relevant difference across treatment groups for any of the SAE were reported in the study. Of the 15 SAE, eight were reported as treatment-related (DRL_RI group: 1, Rituxan group: 3, MabThera group: 4). All severe TEAE resolved within 24 weeks except for 1 patient: sudden death) with fatal outcome.

Table 12-4 Listing of Treatment-Emergent Serious Adverse Events (Safety Analysis Population)				
	DRL_RI N=91 n (%) nAE	Rituxan N=92 n (%) nAE	MabThera N=93 n (%) nAE	Total N=276 n (%) nAE
Number of patients with at least 1 treatment-emergent SAE	2 (2.2) 2	4 (4.3) 5	6 (6.5) 8	12 (4.3) 15
Infections and infestations	1 (1.1) 1	0	2 (2.2) 2	3 (1.1) 3
H1N1 influenza	0	0	1 (1.1) 1	1 (0.4) 1
Pneumonia	1 (1.1) 1	0	0	1 (0.4) 1
Urinary tract infection	0	0	1 (1.1) 1	1 (0.4) 1
Injury, poisoning and procedural complications	0	2 (2.2) 2	1 (1.1) 2	3 (1.1) 4
Femoral neck fracture	0	0	1 (1.1) 1	1 (0.4) 1
Forearm fracture	0	0	1 (1.1) 1	1 (0.4) 1
Humerus fracture	0	1 (1.1) 1	0	1 (0.4) 1
Infusion related reaction	0	1 (1.1) 1	0	1 (0.4) 1
Blood and lymphatic system disorders	0	2 (2.2) 2	0	2 (0.7) 2
Febrile neutropenia	0	1 (1.1) 1	0	1 (0.4) 1
Neutropenia	0	1 (1.1) 1	0	1 (0.4) 1
Cardiac disorders	0	0	2 (2.2) 2	2 (0.7) 2
Atrial fibrillation	0	0	1 (1.1) 1	1 (0.4) 1
Cardio-respiratory arrest	0	0	1 (1.1) 1	1 (0.4) 1
General disorders and administration site conditions	1 (1.1) 1	0	1 (1.1) 1	2 (0.7) 2
Pyrexia	0	0	1 (1.1) 1	1 (0.4) 1
Sudden death	1 (1.1) 1	0	0	1 (0.4) 1
Gastrointestinal disorders	0	1 (1.1) 1	0	1 (0.4) 1
Intestinal obstruction	0	1 (1.1) 1	0	1 (0.4) 1
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.1) 1	1 (0.4) 1
Interstitial lung disease	0	0	1 (1.1) 1	1(0.4) 1

During Part 2 (i.e. between Wk 24 and Wk 52), 6 SAE were reported in 6 (2.2%) patients (DRL_RI group: 1 [1.1%]; Rituxan group: 1 [1.1%]; and MabThera group: 4 [4.3%]) during the study. A total of 3 (all in the MabThera arm) of the 6 SAE were judged related to the study drug. Five of the 6 SAE were non-fatal; however, 1 patient from the DRL_RI arm died post Week 24; due to unknown cause of sudden death).

Table 52 List of Treatment Serious Adverse emergent events (Safety analysis population)

	DRL_RI N=91 n (%) nAE	Rituxan N=92 n (%) nAE	MabThera N=93 n (%) nAE	Total N=276 n (%) nAE
Number of patients with at least 1 treatment-emergent SAE	1 (1.1) 1	1 (1.1) 1	4 (4.3) 4	6 (2.2) 6
Infections and infestations	0	0	3 (3.2) 3	3 (1.1) 3
Cellulitis	0	0	1 (1.1) 1	1 (0.4) 1
Gastroenteritis viral	0	0	1 (1.1) 1	1 (0.4) 1
Pyelonephritis acute	0	0	1 (1.1) 1	1 (0.4) 1
General disorders and administration site conditions	1 (1.1) 1	0	0	1 (0.4) 1
Death	1 (1.1) 1	0	0	1 (0.4) 1
Injury, poisoning and procedural complications	0	1 (1.1) 1	0	1 (0.4) 1
Spinal cord compression fracture	0	1 (1.1) 1	0	1 (0.4) 1
Musculoskeletal and connective tissue disorder	0	0	1 (1.1) 1	1 (0.4) 1
Spondylolisthesis	0	0	1 (1.1) 1	1 (0.4) 1

Abbreviations: N: Number of patients within each treatment arm under safety analysis population; n: Number of patients meeting the event; nAE - Number of adverse events; PT: preferred term; SAE: Serious adverse event; SOC: System Organ Class.
Adverse Event terms are coded by SOC and PT using MedDRA version 19.1.
Patients experiencing multiple events within the same SOC or PT are counted only once under those categories.
Percentages are based on number of patients within each treatment arm under safety analysis population (N).
Ongoing AEs during Part 1 is also presented.
Data for Part 2 is considered. Post Week 24 visits is considered as Part 2.

Two deaths occurred during the study, one during Part 1 and one during Part 2. Both deaths occurred in the DRL_RI arm, were however judged unrelated.

A patient with RA randomized to RI-01-003 study died 154 days after first infusion of study drug and another patient with RA died 353 days after first infusion. In both cases no autopsy was performed and the cause of death was reported as unknown; the Investigator considered the event of sudden death (severe) to be unrelated to study drug.

Infusion related reactions occurred in overall 4 patients (1.4%; 4 events) during Part 1 of the study, with DRL_RI: 1 event in 1 [1.1%] patient, Rituxan: 2 events in 2 [2.2%] patient, and MabThera: 1 event in 1 [1.1%] patient.

Single transition trial RI-01-007

A total of 4 (5.7%) subjects in the DRL_RI group and 2 (2.9%) subjects in the Rituxan or MabThera group experienced overall 9 treatment-emergent SAE during the study.

SAE reported in the DRL_RI group by PT were COVID-19 pneumonia (2 [2.9%] subjects), myocardial infarction and intestinal resection (1 [1.4%] subject, each). None of these SAE were considered related to the study drug.

Of these SAE, only the event of embolic stroke was considered related to the study drug.

Seven of the overall 9 SAE resolved without sequelae, 1 SAE (embolic stroke) resolved with sequelae (cane support to walk), and 1 SAE (COVID-19 pneumonia) was fatal.

Table 3-10 Serious Treatment-Emergent Adverse Events in Study RI-01-007 by Preferred Term (Safety Population)

Preferred Term	DRL_RI (N=70) n (%) (e)	US-rituximab or EU-rituximab (N=70) n (%) (e)	Total (N=140) n (%) (e)
Number of subjects with at least 1 serious TEAE	4 (5.7) (4)	2 (2.9) (5)	6 (4.3) (9)
COVID-19 pneumonia	2 (2.9) (2)	0	2 (1.4) (2)
Cystitis	0	1 (1.4) (1)	1 (0.7) (1)
Empyema	0	1 (1.4) (1)	1 (0.7) (1)
Septic shock	0	1 (1.4) (1)	1 (0.7) (1)
Myocardial infarction	1 (1.4) (1)	0	1 (0.7) (1)
Enteritis	0	1 (1.4) (1)	1 (0.7) (1)
Embolic stroke	0	1 (1.4) (1)	1 (0.7) (1)
Intestinal resection	1 (1.4) (1)	0	1 (0.7) (1)

Abbreviations: COVID-19 = coronavirus disease 2019; DRL_RI = Dr. Reddy's rituximab; EU-rituximab = European Union approved rituximab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the Safety Analysis Set; TEAE = treatment-emergent adverse event; US-rituximab = United States licensed rituximab (Rituxan).

As stated above, one death occurred in the DRL_RI arm of this trial. A subject with RA was randomly assigned to the DRL_RI treatment group and received the last dose of the study drug on Day 15. The subject had received 7 prior treatment courses with MabThera before initiating treatment in this study. On Day 179 an SAE of COVID-19 pneumonia was confirmed and on Day 208, the subject died due to the event of COVID-19 pneumonia. The Investigator assessed this event as not related to study drug.

With regard to AESI, 1 TEAE of Grade 2 hypersensitivity was reported in 1 subject in the MabThera/Rituxan arm. In the DRL_RI arm, 2 TEAE of Grade 1 IRR were reported in 2 subjects.

2.6.8.4. Laboratory findings

Phase 3 LTB-FL study RI-01-006

There were no obvious differences between the treatment arms in haematology parameters.

Cases of mild lymphopenia were reported in this study, as may be expected considering the mode of action of rituximab. As reported before for rituximab (see SmPC MabThera), neutropenia was reported in the submitted study as well. However, both for lympho- and neutropenia, severe cases were rare, and balanced over the groups.

Overall, no clinically meaningful differences were observed for clinical chemistry parameters between the treatment arms. Shifts observed from baseline to CTCAE Grade 3 in biochemistry parameters included potassium decreased and sodium decreased.

With regard to potential liver hepatotoxicity, a review of Hy's Law analytic was conducted and any results meeting drug-induced liver injury criteria for Hy's Quadrant and Temple's Corollary were tracked for correlation with the subject's safety.

According to the applicant, as of Week 28 there were 5 Temple's Corollary present in the study, three subjects in the MabThera group and two in the DRL_RI treatment group; however, there were no safety issues observed during the study.

Some shifts were observed in urinalysis parameters. Overall, no clinically relevant imbalances between the treatment arms were detected.

With regard to vital signs, systolic and diastolic BP, heart rate, respiratory rate, and body temperature values were overall comparable between treatment arms. No clinically relevant differences were detected.

All subjects had normal or abnormal, not clinically significant ECG results at all time points during the study.

At Screening, one subject in the DRL_RI group had abnormal, clinically significant ECG results (i.e. a prolonged PR interval) due to a medical history of right bundle branch blockade of his bundle G1. No abnormal clinically significant ECG results were reported in MabThera group at any time point during the study.

No relevant imbalances were observed between the treatment arms with regard to physical examination.

PK equivalence study RI-01-003

Haematology data were collected at Week 36 and Week 52. At these time points, there were no clinically meaningful changes in mean values for haematology between the 3 treatment groups.

There were no clinically meaningful differences in mean values from baseline during the study for clinical chemistry parameters between the 3 treatment arms from the start of treatment administration until the end of study visit at 52 week.

There were no clinically meaningful changes observed from baseline during the study for urinalysis parameters between the treatment arms.

Vital signs were assessed up to Week 24 of the study. No clinically relevant differences were observed between the treatment groups.

ECG was performed as part of screening for assessing the eligibility of the patients and was not assessed after the initiation of treatment.

There were no clinically relevant changes in the physical examination findings across all time points for all 3 treatment groups up to Week 24 of the study.

In addition, the relationship between study drug administration and risk of reactivation of latent tuberculosis infection in RA patients was explored. No reactivation or new cases of tuberculosis were reported up to Week 24 of the study.

Single transition study RI-01-007

No obvious differences or clinically relevant changes were observed for haematology parameters for the different treatment arms. Only a few subjects in both treatment arms experienced shifts to Grade 3 or higher in haematology parameters.

No obvious clinically relevant changes or differences between the treatment arms were observed with regard to biochemistry parameters.

No apparent treatment-related changes or differences between the treatment arms were detected with regard to urine parameters.

Overall, no clinically relevant differences were observed with regard to vital signs between the treatment arms. One abnormal vital signs examination finding was reported as a TEAE. This was non-serious hypertension in one subject in the Rituxan/ MabThera arm; this event resolved during the study.

No apparent treatment-related trend or clinically relevant changes were observed with regard to ECG parameters. Abnormal shifts in ECGs from baseline were reported at Week 12 and Week 26 in individual subjects; however, none was reported as clinically significant.

The majority of subjects had normal baseline physical examination results that remained normal at each time point. There were no notable differences between the treatment groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

N/A

2.6.8.7. Immunological events

Immunogenicity

The immunogenicity of DRL_RI has been compared with MabThera and Rituxan in RA patients in studies RI-01-003 and RI-01-007 (transition study) and in LTB-FL patients in study RI-01-006. As part of the immunogenicity strategy for the clinical development of DRL_RI, pre-treatment and post-dose samples were collected in all clinical trials.

Immunogenicity status was determined for immunogenicity evaluable subjects who were defined as those with at least one post-dose anti-drug antibody (ADA) assay result. Post-dose samples were defined as samples collected after administration of study drug.

In studies RI-01-003, RI-01-006, and RI-01-007, analysis of ADA samples followed a tiered approach of screening, confirmation, and titre determination. Samples that were confirmed positive for ADA were further tested for titre and neutralising antibodies (NAb) using validated assays.

ADA titres were measured by an ELISA that was based on pre-treatment of samples and detection of immune complexes dissociated by acid. NAbs were detected by a cell-based assay utilizing human B lymphocyte cells, WIL2-S, as responding cells and the changes of cell viability by CDC as the method endpoint.

Continuous data were described using descriptive statistics (i.e., n, mean, standard deviation [SD], median, quartiles, minimum, and maximum). Categorical data were described using the count and percentage in each category.

Immunogenicity in RA patients

Immunogenicity of DRL_RI compared to MabThera and Rituxan in RA patients was assessed in studies RI-01-003 (inherent immunogenicity) and RI-01-007 (transition immunogenicity).

Blood samples for immunogenicity assessment were collected at Week 0, 4, 16, 24 (Part 1), and Week 52 (Part 2) in study RI-01-003, and at Day 0, Day 1, Day 15, Weeks 4, 8, and 12 in study RI-01-007. The incidence and titre of ADA, including incidence of NAbs, were evaluated at each time point.

Trial inclusion/exclusion criteria in both RA trials was selected to ensure safety of trial patients and assay sensitivity for efficacy assessment. Specifically, patients were excluded if they had used immunosuppressants such as alkylating agents or azathioprine, prior rituximab (in study RI-01-003),

abatacept, tocilizumab, anakinra or another agent/antibody targeting CD20, CD19 or B-cells, tumour necrosis factor (TNF) alfa antagonists or other biologic DMARDs, or leflunomide therapy within 3 months of screening – thus selected patients were immunocompetent and difference in immunogenicity could be easily detected.

Administration of rituximab is contraindicated for patients in a severely immunocompromised state, thus the trials excluded patients suffering from human immunodeficiency virus, tuberculosis, systemic infection, or having weakened immune system. In line with prescribing information, patients who had history of hypersensitivity to Rituxan or MabThera were excluded from the study.

Study RI-01-003

The proportion of ADA positive patients was comparable at Baseline (Week 0) and up to Week 52 in all study arms. The immunogenicity in the DRL_RI arm was numerically lower, but 95% CIs broadly overlapped as compared to MabThera and Rituxan.

Most of the observed ADA were low and non-neutralizing. The proportion of patients with NAbs was very low ranging from 0–2% and did not appear to differ between treatment arms.

Table 53 Immunogenicity results in study RI-01-003 (Safety population)

Immunogenicity test	DRL_RI	Rituxan	MabThera
	n (%)		
Week 0 (Baseline)			
ADA Positive	3 of 91 (3.3)	2 of 92 (2.2)	0 of 93 (0)
ADA titre, median (minimum-maximum)	1.0 (1–1)	NR	NR
NAb Positive (as % of ADA positive)	0	0	0
Week 4			
ADA Positive	1 of 88 (1.1)	0 of 87 (0)	1 of 83 (1.2)
ADA titre, median (minimum-maximum)	NR	NR	NR
NAb Positive (as % of ADA positive)	0	0	0
Week 16			
ADA Positive	2 of 88 (2.3)	3 of 87 (3.4)	2 of 85 (2.4)
ADA titre, median (minimum-maximum)	8.0 (8–8)	1.0 (1–1)	8.0 (8–8)
NAb Positive (as % of ADA positive)	1 (1.1)	0	1 (1.2)
Week 24			
ADA Positive	4 of 87 (4.6)	12 of 86 (14.0)	7 of 87 (8.0)
ADA titre, median (minimum-maximum)	4.0 (1–8)	1.0 (1–16)	9.0 (1–256)
NAb Positive (as % of ADA positive)	1 (1.1)	1 (1.2)	1 (1.1)
Week 52			
ADA Positive	12 of 82 (14.6)	22 of 80 (27.5)	22 of 82 (26.8)
ADA titre, median (minimum-maximum)	2.0 (1–2)	2.0 (1–16)	1.0 (1–8)
NAb Positive (as % of ADA positive)	0	2 (2.5)	1 (1.2)

Abbreviations: NR = not reported; ADA = anti-drug antibody; NAb = neutralizing antibody; n(%) = number (percentage) of patients.

TEAE by ADA status

Three patients who were ADA positive at Week 52 (all NAb – negative) experienced IRR (one in Rituxan, one in MabThera and one in DRL_RI).

The first patient experienced skin rashes; the second patient experienced itching over the head, ear, and a facial rash. The last patient reported an infusion reaction that included nasal congestion, runny nose, and skin rash.

Study RI-01-007

At baseline, 3 (4.3%) patients in the DRL_RI group and in 1 (1.5%) patient in the Rituxan/MabThera group were tested ADA positive; no patient was tested positive for NAbs. Among these 4 patients being ADA positive at BL, only one patient in the Rituxan/MabThera group remained ADA positive at Week 12.

Overall, 1 patient in the DRL_RI arm and 2 patients in the Rituxan/MabThera arm were tested positive for ADA at Week 12. None of them was tested positive for NAbs at Week 12.

The incidence of ADA after dosing was low in both treatment groups.

Table 54 Immunogenicity results in study RI-01-007 (immunogenicity population)

Visit	DRL_RI (N=69)			Rituxan/MabThera (N=68)		
	ADA n (%)	ADA titre median (Q1–Q3)	NAb n (%)	ADA n (%)	ADA titre median (Q1–Q3)	NAb n (%)
Baseline						
ADA Positive	3 (4.3)	360 (180–720)	0	1 (1.5)	360 (360–360)	0
ADA Negative	65 (94.2)	NA	3 (4.3)	65 (95.6)	NA	1 (1.5)
ADA Missing	1 (1.4)	NA	0	2 (2.9)	NA	0
Day 15						
ADA Positive	1 (1.4)	180 (180–180)	0	0	-	0
ADA Negative	66 (95.7)	NA	1 (1.4)	65 (95.6)	NA	0
ADA Missing	2 (2.9)	NA	0	3 (4.4)	NA	0
Week 4						
ADA Positive	0	-	0	0	-	0
ADA Negative	65 (94.2)	NA	0	62 (91.2)	NA	0
ADA Missing	4 (5.8)	NA	0	6 (8.8)	NA	0
Week 8						
ADA Positive	1 (1.4)	1440 (1440–1440)	1 (1.4)	0	-	0
ADA Negative	63 (91.3)	NA	0	60 (88.2)	NA	0
ADA Missing	5 (7.2)	NA	0	8 (11.8)	NA	0
Week 12 (EOS/EOT)						
ADA Positive	1 (1.4)	720 (720–720)	0	2 (2.9)	540 (360–720)	0
ADA Negative	63 (91.3)	NA	1 (1.4)	62 (91.2)	NA	2 (2.9)
ADA Missing	5 (7.2)	NA	0	4 (5.9)	NA	0

Abbreviations: ADA = anti-drug antibodies; Nab = neutralizing antibodies; EOS = end of study; EOT = end of treatment; Q1 = first quartile; Q3 = third quartile; NA = not applicable.

TEAE by ADA status

An ADA positive at baseline and Week 12 in the Rituxan or MabThera group reported TEAE of COVID-19 on Day 54. In addition, time-matched rituximab concentrations (TMRC) collected in study RI-01-007 indicated that rituximab concentrations were within the drug tolerance of the ADA assays at each time points and did not impact the detection of ADA in the samples.

Immunogenicity in LTB-FL patients

Study RI-01-006

Immunogenicity of DRL_RI as compared to MabThera in LTB-FL patients was assessed as part of the secondary objectives in study RI-01-006. Blood samples were collected at Weeks 0, 4, 8, 28, as well as at visits of Week 44 and Week 52 (the present study dossier and CSR presents data up to Week 28). Immunogenicity analysis set included all randomized participants with at least one immunogenicity sample with a valid result.

The majority of patients in both treatment arms had negative ADA results. The proportion of patients with positive ADA results at post-treatment was comparable in both the treatment groups. A total of 9 patients (2.8%); 7 subjects (4.4%) in DRL_RI group and 2 subjects (1.6%) in the MabThera group had at least 1 positive ADA result at post treatment visits.

Out of these 7 subjects in the DRL_RI group with positive ADA results, 2 subjects had ADA positive results that were transient at Week 4 and Week 8, and the results turned negative at Week 28. However, the ADA in the remaining of the 5 subjects remained positive at Week 28 (two subjects with a titer value of <1.00). One subject in the DRL_RI group had positive NAb result at Week 8 and Week 28 and reported an IRR at Week 4.

Table 12 Immunogenicity Results in study RI-01-006 (Immunogenicity Analysis Set)

Visit	DRL_RI (N=160)			MabThera (N=152)		
	ADA n (%)	ADA titre Median (min–max)	NAb n (%)	ADA n (%)	ADA titre median (min–max)	NAb n (%)
Baseline						
ADA Positive	0	NC	0	0	NC	0
ADA Negative	154 (96.3)	NA	0	150 (98.7)	NA	0
ADA Missing	6 (3.8)	NA	160 (100)	2 (1.3)	NA	152 (100)
Week 4						
ADA Positive	3 (1.9)	80.0 (1–160)	0	0	NC	0
ADA Negative	151 (94.4)	NA	3 (1.9)	146 (96.1)	NA	0
ADA Missing	6 (3.8)	NA	157 (98.1)	6 (3.9)	NA	152 (100)
Week 8						
ADA Positive	2 (1.3)	5120.5 (1–10240)	1 (0.6)	1 (0.7)	640 (640–640)	0
ADA Negative	151 (94.4)	NA	1 (0.6)	144 (94.7)	NA	1 (0.7)
ADA Missing	7 (4.4)	NA	158 (98.8)	7 (4.6)	NA	151 (99.3)
Week 28						
ADA Positive	5 (3.1)	160.0 (1–4096)	1 (0.6)	2 (1.3)	2600 (80–5120)	0
ADA Negative	137 (85.6)	NA	4 (2.5)	126 (82.9)	NA	2 (1.3)
ADA Missing	18 (11.3)	NA	155 (96.9)	24 (15.8)	NA	150 (98.7)

Abbreviations: ADA = anti-drug antibodies; NAb = neutralizing antibodies; NC = non-calculable; NA = not applicable; N = total number of patients, n = number of patients with available data.
Source: Study RI-01-006 Primary CSR-28 January 2023, Table 14.3.4.2.1, Table 14.3.4.2.2 (Section 5.3.5.1.1)

TEAE by ADA status

Five (1.6%) subjects who were ADA positive experienced a TEAE - 4 [2.5%] subjects in the DRL_RI group, and 1 [0.7%] subject in the MabThera group. One subject in DRL_RI group experienced the AE of IRR (during the induction treatment period) which was considered as related to study treatment.

Table 55 Summary of Treatment emergent adverse events by ADA status, SOC and PT in RI-01-006 (Safety population)

System Organ Class Preferred Term	DRL RI (N=162) n (%) E	MabThera (N=153) n (%) E	Overall (N=315) n (%) E
No. of subjects with at least one TEAE	4 (2.5) 8	1 (0.7) 1	5 (1.6) 9
Blood and lymphatic system disorder	1 (0.6) 1	1 (0.7) 1	2 (0.6) 2
Anaemia	0	1 (0.7) 1	1 (0.3) 1
Lymph node pain	1 (0.6) 1	0	1 (0.3) 1
Infections and infestations	2 (1.2) 3	0	2 (0.6) 3
Infection	1 (0.6) 1	0	1 (0.3) 1
Oral herpes	1 (0.6) 1	0	1 (0.3) 1
Upper respiratory tract infection	1 (0.6) 1	0	1 (0.3) 1
Injury, poisoning and procedural complications	1 (0.6) 1	0	1 (0.3) 1
Infusion-related reaction	1 (0.6) 1	0	1 (0.3) 1
Investigations	1 (0.6) 3	0	1 (0.3) 3
Alanine aminotransferase increased	1 (0.6) 1	0	1 (0.3) 1
Blood pressure increased	1 (0.6) 1	0	1 (0.3) 1
Gamma-glutamyltransferase increased	1 (0.6) 1	0	1 (0.3) 1

Abbreviations: AE = adverse event; DRL_RI = Dr. Reddy's rituximab; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reporting at least one AE in each category; N = the number of subjects in the Safety Analysis Set; TEAE = treatment-emergent adverse event.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator (n/N*100).
All adverse events were coded using MedDRA version 25.0.
Treatment-emergent adverse events included any AEs occurring or worsening on or after the first dose of study medication.

As already stated above, only 1 subject in the DRL_RI group had a positive NAb result at Week 8 and Week 28 and reported an IRR at Week 4.

Overall immunogenicity across indications

Immunogenicity responses were comparable between DRL_RI, MabThera, and Rituxan in all three studies. Data indicated that DRL_RI induced ADA in only a very small proportion of patients which was similar to MabThera and Rituxan. Most of the detected ADA were non-neutralizing and low in titre.

Table 56 Comparison of Immunogenicity results from clinical studies

Visit	DRL_RI	Rituxan	MabThera
	n (%)		
Study RI-01-006			
Baseline			
ADA Positive	0	NA	0
NAb Positive	0	NA	0
Week 28			
ADA Positive	5 of 160 (3.1)	NA	2 of 152 (1.3)
NAb Positive	1 of 160 (0.6)	NA	0
Study RI-01-003			
Baseline			
ADA Positive	3 of 91 (3.3)	2 of 92 (2.2)	0 of 93 (0)
NAb Positive	0	0	0
Week 52			
ADA Positive	12 of 82 (14.6)	22 of 80 (27.5)	22 of 82 (26.8)
NAb Positive	0	2 (2.5)	1 (1.2)
Study RI-01-007[a]			
Baseline			
ADA Positive	3 of 69 (4.3)	1 of 68 (1.5)	
NAb Positive	0	0	
Week 12			
ADA Positive	1 of 69 (1.4)	2 of 68 (2.9)	
NAb Positive	0	0	

Abbreviations: ADA = anti-drug antibodies; NAb = neutralizing antibodies; NA = not applicable. [a]Rituxan or MabThera for Study RI-01-007.

2.6.8.8. Safety related to drug-drug interactions and other interactions

N/A

2.6.8.9. Discontinuation due to adverse events

In the **Phase 3 LTB-FL study RI-01-006**, 3 subjects discontinued due to 3 TEAE.

One subject in the DRL_RI group discontinued due to Grade 3 COVID-19 pneumonia. The TEAE of COVID-19 pneumonia was considered serious, not related to the study drug, and recovered/resolved.

Two subjects in the MabThera group discontinued due to Grade 3 squamous cell carcinoma and Grade 3 psychomotor hyperactivity. The TEAE of squamous cell carcinoma was considered serious, not related to the study drug, and not recovered/not resolved. The TEAE of psychomotor hyperactivity was considered as serious, related to the study drug, and did not recover/not resolve.

In the **PK equivalence study RI-01-003**, a total of 10 patients discontinued the study due to TEAE during Part 1 (DRL_RI: 1 patient with 1 event, Rituxan: 3 patients with 3 events, MabThera: 6 patients with 6 events). The AEs leading to study discontinuation were H1N1 influenza, herpes simplex, upper respiratory tract infection, choking sensation, interstitial lung disease, rash, urticaria, cardio-respiratory arrest, sudden death, and an infusion-related reaction.

During Part 2 of the study, another 2 patients (1 patient with 1 event in both the DRL_RI and the Rituxan arm) discontinued the study due to TEAE. The AEs leading to study discontinuation were death and spinal compression fracture.

TEAE leading study discontinuation in the **single transition trial RI-01-007** were drug hypersensitivity in 1 subject in the DRL_RI group and hypersensitivity in 1 subject in the Rituxan or MabThera group. Both events resolved during the study. The event of drug hypersensitivity was considered not related to the study drug, and the event of hypersensitivity was considered related to the study drug.

2.6.8.10. Post marketing experience

DRL anti-CD20 monoclonal antibody (rituximab) was initially approved in India under the brand name "Reditux" on 22 March 2007. Currently, the product is approved and/or available in many countries under brand names Reditux, Reditux RA, and Redditux for the treatment of NHL, CLL, RA, granulomatosis with polyangiitis, microscopic polyangiitis and PV.

During the pre-submission meeting, it has been outlined by the applicant that there are "slight differences" in the manufacturing process between DRL_RI and Reditux. Thus, the post-marketing data for Reditux are not considered relevant for the current submission.

2.6.9. Discussion on clinical safety

Three clinical studies were conducted to compare the safety profiles of DRL_RI and MabThera; two in the RA indication, one in the LTB-FL indication.

The pivotal comparative efficacy & safety Phase 3 study RI-01-006 was conducted in Europe, India, South Korea and in the US, including a total of 317 subjects diagnosed with previously untreated Stage II-IV, CD20 positive LT-BFL. Patients received rituximab at a dose of 375 mg/m^2 i.v. (either DRL_RI or MabThera) with 4 weekly doses in the induction phase, followed by a maintenance phase consisting of another 4 rituximab i.v. infusion every 8 weeks, starting from Wk 12 until Wk 36.

In addition, a 3-way PK equivalence study (RI-01-003) was conducted in India and in Ukraine comparing DRL_RI to Rituxan and MabThera in combination with non-biological disease-modifying antirheumatic drugs (DMARDs) in 276 patients with moderate to severe active RA. Patients received two infusions of rituximab at a dose of 1000 mg on Day 1 and on Day 15.

Furthermore, safety data from a Phase 3 single switch transition trial (RI-01-007) were included. In this study conducted in Europe and in the US, 140 patients with active RA who had received at least 1 full treatment course (1000 mg rituximab i.v. on D1 and D15) with either MabThera or Rituxan before were then either switched to receive a second rituximab treatment course with DRL_RI (n=70) or continued with MabThera/ Rituxan (n=70).

Key safety information was derived from the Phase 3 study RI-01-006, supported by safety and tolerability data from the studies RI-01-003 and RI-01-007.

In addition, safety data from another clinical trial, namely study RI-01-002 conducted in CD20-positive DLBCL patients with Reditux in India, were presented, to provide transparency with regard to the full set of clinical data available. The applicant states that study RI-01-002 was conducted for supporting approval in emerging market countries and hence is considered as supportive only. Study RI-01-002 underwent multiple changes during execution; furthermore, it has been outlined by the applicant that there are "slight differences" in the manufacturing process between DRL_RI and Reditux. Thus, from the Rapporteur´s point of view, those data are not considered relevant for the current submission.

As part of the clinical similarity exercise, safety data was available for both a non-oncology and an oncology indication (RA: RI-01-003, RI-01-007 and LTB-FL: RI-01-006). This is endorsed.

Administration of the study drugs was in accordance with the anticipated approved posology for MabThera.

The safety analysis period was 52 weeks in studies RI-01-003 and RI-01-006, and 26 weeks in study RI-01-007. However, the treatment period was 36 weeks in the Phase 3 study (RI-01-006), with a follow-up period until Wk 52. This is considered adequate to assess safety and immunogenicity in a biosimilarity exercise.

Safety was assessed based on the occurrence of adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAE) categorised by SOC and PT and coded by MedDRA as well as any changes in vital signs, clinical laboratory assessment, physical examination and immunogenicity. The safety population in each study included all patients who received at least one dose of IMP.

Overall, 323 patients were exposed to DRL_RI in the clinical development program: 162 LTB-FL patients from study RI-01-006, 91 rituximab-naïve RA patients from study RI-01-003, and 70 rituximab-exposed RA patients from study RI-01-007.

The safety database size is considered rather small, and only provides insight in common AEs. For a biosimilar application, the numbers of subjects are considered acceptable.

Adverse events

In the Phase 3 LTB-FL study RI-01-006, a total of 530 AE occurred in 197 subjects (62.5%), with 248 events in 100 subjects in the DRL_RI group (61.7%) and 282 events in 97 subjects in the MabThera group (63.4%).

The incidence and severity of the reported TEAE was generally comparable between the treatment arms (. TEAE were mainly mild or moderate by severity. There were no distinct differences observed between treatment arms.

The most frequently reported TEAE were in the SOC of infections and infestations followed by skin and subcutaneous tissue disorders. The most frequently reported TEAE by Preferred Terms were COVID-19 infections followed by pruritus (. No imbalances regarding TEAE types/ categories were observed between biosimilar and RMP.

Numbers of TEAE judged related to study drug were comparable between both treatment arms.

The incidence of infusion related AEs was comparable between treatment arms.

There were no relevant imbalances detected in the severity grade of IRR between the biosimilar candidate and the reference product, MabThera.

For the PK equivalence study RI-01-003, safety data are reported separately for Part 1 (until Week 24) and for Part 2 (from Week 24 until Week 52).

During Part 1, the numbers of subjects that experienced at least one TEAE was comparable between study arms. The numbers of TEAE as well as of TEAE judged related to study drug were overall comparable between study arms, with a higher incidence of related TEAE in the MabThera arm.

The most commonly reported TEAEs related to study drug were infusion related reactions.

Majority of the TEAE reported in the study were mild in severity and few TEAE were classified as severe. Their incidences were comparable between the treatment arms. All severe TEAEs resolved within 24 weeks except for 1 patient in the DRL_RI arm: sudden death) with a fatal outcome.

During Part 1 of the study, the most frequently reported TEAE by PT were upper respiratory tract infection (SOC Infections and infestations), cough (SOC Respiratory, thoracic and mediastinal disorders), and pyrexia (SOC General disorders) with no distinct imbalances between treatment groups.

Incidences of TEAE were also comparable between treatment arms during Part 2 of the study, with few treatment-related TEAE reported.

The majority of the TEAE reported ongoing at the end of Part 1 or reported in Part 2 of the study were considered as mild in severity. All severe TEAE post Week 24 resolved during the study except for 1 event in 1 patient in the DRL_RI arm: sudden death) with fatal outcome.

The most frequently reported TEAE by PT after Week 24 were evenly distributed across the treatment groups: B lymphocyte count decreased (SOC Investigations), rheumatoid arthritis (SOC Musculoskeletal and connective tissue disorders), upper respiratory tract infection (SOC Infections and infestations), cough (SOC Respiratory, thoracic and mediastinal disorders), and pyrexia (SOC General disorders).

In the single transition trial RI-01-007, TEAE were reported in 24 patients (34.3%; 35 events) in the DRL_RI arm and in 27 patients (38.6%; 54 events) in the MabThera/Rituxan arm. Only few TEAE were of Grade 3 or higher (5 events in 4 subjects in the DRL_RI arm vs. 5 events in 2 subjects in the MabThera/Rituxan arm). Only 3 events in 3 subjects in the DRL_RI arm and 7 events in 4 subjects in the MabThera/Rituxan arm were considered treatment-related.

The most commonly reported (>3% of subjects overall) TEAE were attributed to the SOCs Infections and infestations, Gastrointestinal disorders, Nervous system disorders, and Musculoskeletal and connective tissue disorders. Treatment-emergent AEs were more commonly reported in the Rituxan or MabThera group than in the DRL_RI group with regard to these SOCs of Infections and infestations (18.6% of subjects vs. 8.6% of subjects), Gastrointestinal disorders (8.6% of subjects vs. 4.3% of subjects), Nervous system disorders (8.6% of subjects vs. 1.4% of subjects), and Musculoskeletal and connective tissue disorders (4.3% of subjects vs. 2.9% of subjects, respectively).

The most common TEAE by PT reported (>3% of subjects) in the Rituxan or MabThera group included diarrhoea and headache, and COVID-19 and nasopharyngitis. No AE by PT was reported in more than 3% of subjects in the DRL_RI group.

SAE and deaths

During the Phase 3 LTB-FL study RI-01-006, a total of 30 treatment-emergent SAEs were reported in 26 subjects (8.3%) . There were no imbalances in SAE incidence between treatment.

The most frequently reported SAE were in the SOC of Infections and infestations. Overall, 18 events were reported in 17 (5.4%) subjects; 11 events in 10 (6.2%) subjects occurred in the DRL_RI group compared to 7 events in 7 (4.6%) subjects in the MabThera group.

The most frequently reported SAE by PT was COVID-19 pneumonia. Overall, 9 events were reported in 9 (2.9%) subjects; 6 events in 6 (3.7%) subjects occurred in the DRL_RI group and 3 events in 3 (2.0%) subjects occurred in the MabThera group.

Five study drug-related SAE were reported in 5 (1.6%) subjects; 2 events in 2 (1.2%) subjects in the DRL_RI group and 3 events in 3 (2.0%) subjects in the MabThera group.

Overall, 5 deaths were reported in this study, 3 in the DRL_RI arm (1 COVID-19 pneumonia, 2 COVID-19 infections leading to death; and 2 in the MabThera arm (1 COVID-19 pneumonia, 1 pneumonitis). None of the fatal cases was judged related to study treatment.

One death was reported until the Week 28 cut-off date for primary analysis, the other 4 deaths occurred before database lock, however were not reported in the primary analysis.

With regard to AESI, a total of 94 IRR were reported in 60 (19.0%) subjects during the study. The incidence of infusion-related AE was comparable between treatment arms.

During Part 1 of the PK equivalence study RI-01-003, 15 SAE were reported in 12 (4.3%) patients (DRL_RI group: 2 [2.2%], Rituxan group: 4 [4.3%], MabThera group: 6 [6.5%]). No relevant difference across treatment groups for any of the SAE were reported in the study. Of the 15 SAE, eight were reported as treatment-related (DRL_RI group: 1, Rituxan group: 3, MabThera group: 4). All severe TEAE resolved within 24 weeks except for 1 patient: sudden death) with fatal outcome.

During Part 2 (i.e. between Week 24 and Week 52), 6 SAE were reported in 6 (2.2%) patients (DRL_RI group: 1 [1.1%]; Rituxan group: 1 [1.1%]; and MabThera group: 4 [4.3%]) during the study. A total of 3 (all in the MabThera arm) of the 6 SAE were judged related to the study drug. Five of the 6 SAE were non-fatal; however, 1 patient from the DRL_RI arm died post Week 24; due to unknown cause of sudden death).

Overall, 21 SAE were reported from study RI-01-003. All of them, except for 2 SAE, resolved by the EOS visit. The two SAE that did not resolve had fatal outcome (sudden death;: unknown cause of death). Both occurred in the DRL_RI arm and were assessed as unrelated to study drug by the investigator.

Two deaths occurred during the study, one during Part 1 () and one during Part 2 (). Both deaths occurred in the DRL_RI arm, and the cause of death was indicated as unknown. They were both judged unrelated to study treatment. This is considered acceptable, since they occurred 154 and 353 days after the first infusion of study drug.

Infusion related reactions occurred in overall 4 patients (1.4%; 4 events) during Part 1 of the study, with DRL_RI: 1 event in 1 [1.1%] patient, Rituxan: 2 events in 2 [2.2%] patient, and MabThera: 1 event in 1 [1.1%] patient.

During the single transition trial RI-01-007, a total of 4 (5.7%) subjects in the DRL_RI group and 2 (2.9%) subjects in the Rituxan or MabThera group experienced overall 9 treatment-emergent SAE.

SAE reported in the DRL_RI group by PT were COVID-19 pneumonia (2 [2.9%] subjects), myocardial infarction and intestinal resection (1 [1.4%] subject, each). None of these SAE were considered related to the study drug.

Regarding the transition trial RI-01-007, overall 2 subjects from the Rituxan/ MabThera arms experienced 5 SAE (1 subject experienced the SAE Embolic Stroke, the other one experienced the SAE's Enteritis, Cystitis, Empyema and Septic shock).

Of these SAE, only the event of embolic stroke was considered related to the study drug.

Seven of the overall 9 SAE resolved without sequelae, 1 SAE (embolic stroke) resolved with sequelae (cane support to walk), and 1 SAE (COVID-19 pneumonia) was fatal.

As stated above, one death occurred in the DRL_RI arm of this trial. The subject experienced an SAE of COVID-19 pneumonia and died later on. This fatal case was judged not related to study treatment.

With regard to AESI, 1 TEAE of Grade 2 hypersensitivity was reported in 1 subject in the MabThera/Rituxan arm. In the DRL_RI arm, 2 TEAE of Grade 1 IRR were reported in 2 subjects.

Laboratory findings

In the Phase 3 LTB-FL study RI-01-006, there were no obvious imbalances observed between the treatment arms in haematology parameters.

Overall, no clinically meaningful differences were observed for clinical chemistry parameters between the treatment arms.

With regard to potential liver hepatotoxicity, a review of Hy's Law analytic was conducted and any results meeting drug-induced liver injury criteria for Hy's Quadrant and so-called Temple's Corollary were tracked for correlation with the subject's safety.

The applicant clarified that the cut-off for elevated AST and ALT was > 3 times the ULN in order to be classified and reported as "Temple´s Corollary".

In study RI-01-006, 1 subject in the MabThera arm had AST values classified as Temple´s Corollary (i.e. AST > 3x ULN). With regard to ALT, Temple´s Corollary was reported for 3 subjects in the DRL_RI arm and for 2 subjects in the MabThera arm (i.e. ALT > 3x ULN).

Bilirubin levels > 2x ULN were found only in 1 subject in the MabThera arm.

There were no safety issues observed during the study in those patients.

Some shifts were observed in urinalysis parameters. Overall, no clinically relevant imbalances between the treatment arms were detected.

Vital signs were overall comparable between treatment arms. No clinically relevant differences were detected. All subjects had normal or abnormal, not clinically significant ECG results at all time points during the study. No relevant imbalances were observed between the treatment arms with regard to physical examination.

For studies RI-01-003 and RI-01-007, no clinically relevant differences with regard to laboratory findings were observed between the treatment groups.

Discontinuation due to AE

In the Phase 3 LTB-FL study RI-01-006, 3 subjects discontinued due to 3 TEAE.

One subject in the DRL_RI group discontinued due to Grade 3 COVID-19 pneumonia. The TEAE of COVID-19 pneumonia was considered serious, not related to the study drug, and recovered/resolved.

Two subjects in the MabThera group discontinued due to Grade 3 squamous cell carcinoma and Grade 3 psychomotor hyperactivity. The TEAE of squamous cell carcinoma was considered serious, not related to the study drug, and not recovered/not resolved. The TEAE of psychomotor hyperactivity was considered as serious, related to the study drug, and did not recover/not resolve.

In the PK equivalence study RI-01-003, a total of 10 patients discontinued the study due to TEAE during Part 1 (DRL_RI: 1 patient with 1 event, Rituxan: 3 patients with 3 events, MabThera: 6 patients with 6 events). The AEs leading to study discontinuation were H1N1 influenza, herpes simplex, upper respiratory tract infection, choking sensation, interstitial lung disease, rash, urticaria, cardio-respiratory arrest, sudden death, and an infusion-related reaction.

During Part 2 of the study, another 2 patients (1 patient with 1 event in both the DRL_RI and the Rituxan arm) discontinued the study due to TEAE. The AEs leading to study discontinuation were death and spinal compression fracture.

During Part 2 of study RI-01-003, one patient discontinued the study due to the TEAE "death" unknown cause of death on day 353).

TEAE leading study discontinuation in the single transition trial RI-01-007 were drug hypersensitivity in 1 subject in the DRL_RI group and hypersensitivity in 1 subject in the Rituxan or MabThera group. Both events resolved during the study. The event of drug hypersensitivity was considered not related to the study drug, and the event of hypersensitivity was considered related to the study drug.

Overall, the incidence of discontinuations due to AE was low and comparable between the treatment groups.

Immunogenicity

Immunogenicity responses to DRL_RI and to the reference products (MabThera, Rituxan) were overall low and comparable between treatments in the respective studies in RA and LTB-FL patients.

ADA were detected in a lower proportion of patients in DRL_RI treated patients in study RI-001-003, compared to MabThera treated patients - at Week 24, ADA were detected in a total of 4.6% of patients in the DRL_RI and 8.0% patients in the MabThera arm. However, the proportion of ADA positive patients at any time up to Week 24 was higher in DRL_RI treated patients, compared to MabThera treated patients (11.0% vs 8.6%) (5.40 - 19.28) in the DRL_RI arm, 16.3% (9.42 – 25.46) in the Rituxan arm and 8.6% (3.79 – 16.25) in the MabThera arm.

There was no clear relationship between ADA formation and PK, PD and safety. The relationship between ADA and efficacy was not investigated. As there was no influence on PK and safety detected, and considering that ADA formation was overall low and balanced between DRL_RI and the innovator reference products, there is no need to evaluate the relationship between similarity of efficacy and ADA further.

Only few ADA positive serum sample in any of the studies tested positive for NAb. There was no evidence that immunogenicity had an impact on the safety or on the exposure of DRL_RI.

When subjects switched treatment from licensed rituximab to DRL_RI in study RI-01-007, no notable differences in the percentage of ADA positive subjects was observed across treatment groups.

A total of 11 subjects had at least 1 positive ADA result during study RI-01-006, 8 subjects in the DRL_RI arm and 3 subjects in the MabThera arm.

Of the 8 subjects tested ADA-positive in the DRL_RI arm, 6 subjects reported 10 TEAE (one was grade 3 and rest all were grade 2 or 1 in severity) during the study. Of these 10 TEAE, 5 were assessed by investigator as related to the study drug administration, and one SAE was reported. All the TEAE resolved except, one which was reported as weight gain.

In the MabThera arm, 2 out of 3 subjects reported 3 TEAE (one was grade 3, the others were grade 2 or 1 in severity) during the study. Of these 3 TEAE, none was assessed by investigator as related to the study drug administration. One was a SAE with fatal outcome (Pneumonia). The other two TEAE were reported as resolved.

Overall, there is no evidence for a causal relationship between positive ADA status and the occurrence of treatment-related TEAE.

2.6.10. Conclusions on the clinical safety

In general, the nature, incidence and severity of treatment-emergent AE were comparable between the biosimilar product and the reference product, MabThera. There were no new safety signals or unexpected findings identified.

Immunogenicity responses to DRL_RI and to the reference products (MabThera, Rituxan) were overall low and comparable between treatments in the respective studies in RA and LTB-FL patients.

Overall, the submitted safety data are considered supportive for demonstration of biosimilarity.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 57 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (PML) (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinaemia (Non-oncology indications)
Important potential risks	• None
Missing information	• None

2.7.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 58 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	**Risk Minimisation Measures**
Infections, including serious infections All Indications	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:*

	Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (non-oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications)
Progressive Multifocal Leukoencephalopathy	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, including Magnetic Resonance Imaging scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of rituximab must be permanently discontinued. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (non-oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications).
Hepatitis B Reactivation All Indications	**Routine risk communication**: EU SmPC section 4.4: Special warnings and precautions for use. **Routine risk minimization activities recommending specific clinical measures to address the risk**: Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb- status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information**:

	Medicine's legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures**: None
Hypogammaglobulinaemia non-oncology indications	**Routine risk communication**: EU SmPC section 4.4: Special warnings and precautions for use **RA** EU SmPC Section 4.8: Undesirable effects **GPA/MPA** EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Immunoglobulin levels are recommended to be determined prior to initiating treatment with rituximab. **Other risk minimization measures beyond the Product Information**: *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures**: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update:

Pharmacovigilance plan:

With the first regulatory opportunity the Applicant is requested to align with the reference product's RMP in relation to specific follow-up questionnaires, and add the follow-up questionnaire "off-label use in paediatric patients.

Public Summary of the RMP:

At the next regulatory opportunity, the Applicant is requested to align with the reference product throughout the document including PART VI Summary of the RMP in relation to the previously missing information category "Long-term use in GPA/MPA patients".

The body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP

submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ituxredi (rituximab) is included in the additional monitoring list as it is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Ituxredi has been developed as a biosimilar product of MabThera.

The same indications are claimed as established for the EU innovator product MabThera,

- Non–Hodgkin’s Lymphoma (NHL)
- Chronic Lymphocytic Leukaemia (CLL)
- Rheumatoid Arthritis (RA)

- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

- Pemphigus Vulgaris (PV)

Quality

Ituxredi (DRL_RI) was developed as a biosimilar product to the reference medicinal product MabThera (rituximab) which is the EU sourced reference material and therefore the main comparator. Understanding of the reference product (RP) (US - Rituxan) and reference medicinal product (RMP) (EU - MabThera) was achieved by extensive structural and functional characterisation and structure-function relationships established experimentally, along with a survey of the scientific literature on rituximab to generate a Quality Target Product Profile (QTPP).

Overall, taking into account the totality of the data provided, biosimilarity of Ituxredi with MabThera is considered demonstrated from a quality point of view.

Non-clinical data

Using a stepwise approach, the non-clinical development programme focused on the characterization of the physicochemical properties and functional activity of Ituxredi, the RMP and the RP in order to demonstrate similarity between DRL_RI and the reference products in a battery of comparative biological in vitro studies with respect to Fab- and Fc-mediated activities. The toxicity, pharmacokinetics, pharmacodynamics and immunogenicity of Ituxredi were comparable to those with RP and RMP, therefore biosimilarity was demonstrated.

Clinical data

The clinical program for the rituximab biosimilar Ituxredi (DRL_RI) consists of three studies:

Study RI-01-003 is a randomised, multicentre, double-blind, parallel 3-way PK equivalence study comparing DRL_RI to Rituxan and MabThera in combination with non-biological disease-modifying antirheumatic drugs (DMARDs) in 276 patients with active RA. The study has been completed.

Study RI-01-006 is the pivotal Phase 3 study to compare the efficacy, safety, PK, PD, and immunogenicity of DRL_RI with MabThera in 317 patients with previously untreated, stage II-IV, CD20-positive LTB-FL. The overall design of the study (randomized, multicenter, double-blind, parallel-group) is considered acceptable.

All study data up to and including the Week 28 study visit were included in the initial submission. With regard to subject disposition, all available data up to the cut-off date of 21 September 2022 were included (first subject was screened on 15 May 2019, and the last subject completed the Week 28 visit on 13 September 2022). The final and complete CSR for study RI-01-006 including the full data set was submitted with the responses to the LoQ.

Study RI-01-007 is a randomised, double-blind, parallel group, multicentre single transition Phase 3 study in 140 RA patients who had already completed at least 1 full course of treatment with Rituxan or MabThera to assess the immunogenicity and safety after they were subsequently switched to DRL_RI compared to patients who continued treatment with the respective Rituxan or MabThera. This study was conducted in accordance with US-FDA requirements and is completed. Pharmacodynamics and efficacy were not evaluated in this study.

3.2. Results supporting biosimilarity

Quality

Understanding of the RP and the RMP was achieved by extensive structural and functional characterisation and structure-function relationships established experimentally, along with a survey of the scientific literature on rituximab to generate a QTPP. DRL_RI was well characterised considering the outcome of the reference products. Subsequently, criticality ranking for physicochemical and biological attributes was conducted and the numerical criticality ranking took account of clinical relevance for each attribute. A comprehensive similarity assessment was performed between DRL_RI and RMP batches.

The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its RMP. Overall, the conclusion that DRL_RI, RP, and RMP are similar is agreed. Regarding the observed differences the Applicant expanded the discussion but mainly stressed the fact that the differences are not clinically meaningful as the comparable efficacy, PD, safety, and immunogenicity in patients with moderate-to-severe rheumatoid arthritis in RI-01-003 Phase I clinical study was observed and in the RI-01-006 Phase III clinical study in low tumor burden follicular lymphoma patients efficacy equivalence between DRL_RI and MabThera was demonstrated and safety profile was comparable to that of MabThera.

Overall, taking into account the totality of the data provided, biosimilarity of Ituxredi with MabThera is considered demonstrated from a quality point of view.

Non-Clinical

For the purpose of the functional assessment of Fab mediated binding and functions, ADCC, CDC, CD20 binding and induction of apoptosis were assessed using cell-based assays. CDC assay was performed with various concentrations of DRL_RI, RMP or RP. Fc-mediated binding to C1q, and FcRn implicated in effector functions or pharmacokinetics is similar between DRL_RI, RMP. Binding to other FcγRs [FcγRI, FcγRIIa (R and H), FcγRIIb FcγRIIIb and FcγRIIIa (V and F)] was also evaluated as part of the functional similarity assessment and the results demonstrate that the DRL_RI is considered similar to RMP and RP.

Overall, the analytical comparability assessment indicates that DRL_RI should be considered similar to the RMP EU-rituximab, MabThera.

Clinical

Pharmacology

In the pivotal PK similarity study RI-01-003 in RA patients, DRL_RI, Rituxan and MabThera exhibited similar PK profiles with regard to the primary PK endpoints AUC0-14 days, first infusion, AUC0-inf, entire course, and AUC0-t, second infusion. For the PK similarity comparisons of DRL_RI to each of the reference products (rituximab-EU and rituximab-US), the 91% CIs for the test-to reference ratios of AUC0-14 days, AUC0-inf and AUC0-t were within the bioequivalence acceptance criteria of 80.00% to 125.00%, demonstrating PK similarity among rituximab-US, rituximab-EU, and DRL_RI.

In addition, all other exposure parameters such as Cmax first infusion, Cmax second infusion, and AUC0-t, entire course showed biosimilarity (90% confidence intervals contained within 80.00% to 125.00%).

Primary PK analyses was conducted in the pre-defined PK population including all evaluable patients with PK concentrations without significant protocol deviations and without any confirmed positive test result for ADA.

Sensitivity analyses for the primary endpoints were performed in two populations: in the PK population including ADA positive patients, and in the PK population excluding ADA positive and forced randomization patients. They were supportive for the primary analysis in the original PK population, since their 91% CIs for the ratios of GM met the acceptance criteria of 80.00 to 125.00%.

The sparse drug concentration data for the Phase 3 study RI-01-006 in LTB-FL patients treated with either DRL_RI or MabThera indicate similar rituximab serum concentrations at each time point between the 2 treatment groups and support the conclusion that DRL_RI is biosimilar to MabThera also in this disease population.

In the single transition study RI-01-007 in RA patients, the study objective was to assess the immunogenicity and safety of transitioning subjects with RA from Rituxan/MabThera treatment to either DRL_RI treatment ("switch") or to continued treatment with Rituxan/MabThera.

In this setting, time-matched serum rituximab concentrations (TMRC) were assessed at different time points, along with immunogenicity sampling. Those TMRC values were overall comparable between both treatment groups, DRL_RI and MabThera/Rituxan.

Efficacy

Study RI-01-006

The primary endpoint, BOR up to week 28 based on central radiology review in the ITT population, was 80.25% in the DRL_RI group and 79.35% in the MabThera group. The analysis of BORR showed an estimated difference of 0.89% (DRL_RI minus MabThera), with a 95% CI of (-8.05%, 9.93%), which fell entirely within the pre-specified equivalence margin of ±17%.

Additional analyses based on PPS and investigator assessment as well as all sensitivity analyses (ITT and PPS) have been performed for the primary endpoint, all of which met the equivalence criteria, thus supporting similarity. The differences of BORR for supplementary analyses ranged from -2.68% to 1.39%.

BOR results are overall supporting similarity of DRL_RI to MabThera.

ORR based on central review at week 12 and 28 as well as the proportion of subjects assessed as having CR or PR at week 12 were comparable between the 2 treatment groups.

For the response assessment according to Lugano criteria, responder rates (CR + PR) were similar between the treatment arms as were the concordance rates between Cheson-1999 and Lugano 2014 criteria.

RI-01-003

The change in mean DAS28-CRP scores decreased from Baseline to Week 24 in all 3 treatment arms not indicating clinically meaningful differences between the groups.

The proportion of patients with ACR20, ACR50 and ACR70 response was comparable for Ituxredi and MabThera at week 24.

There were no apparent differences regarding changes from baseline in HAQ-DI and VAS scores.

Safety

Overall, the nature and incidence of the adverse events was balanced between the study arms in the study in LTB-FL as well as in the RA studies. As could be expected given the known safety profile of rituximab, infections and infusion-related reactions were commonly reported. These events were rarely reported to be serious. No new safety signals or unexpected findings were identified.

Immunogenicity responses to DRL_RI and to the reference products (MabThera, Rituxan) were overall low and comparable between treatments in the respective studies in RA and LTB-FL patients.

3.3. Uncertainties and limitations about biosimilarity

Quality

The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its reference medicinal product. Regarding the observed differences that applicant expanded the discussion but mainly stressed the fact that the differences are not clinically meaningful as the comparable efficacy, PD, safety, and immunogenicity equivalence between DRL_RI and MabThera was demonstrated and the safety profile was comparable to that of MabThera

Non-Clinical

See comments on quality.

Clinical

Pharmacology

No uncertainties regarding *PK and PD data*

Efficacy

Study RI-01-006

There is only one study (Ardeshna et al) which forms the basis for the prespecified equivalence margin (±17%) for BORR. However, the Applicant provided a table displaying (B)ORR data from the reference study as well as from historical data with comparable response rates to study RI-01-006. In supplementary analyses where all missing values were treated as responders in one arm and non-responders in the other the margin of ±17% was not met. Concerns regarding a potential negative impact of blinding of trial results were discussed. In parallel to protocol amendment 4 (change of primary endpoint and equivalence margin) the BSSR was conducted to which the Applicant had access to and even more problematic, leading personnel from the Applicant (i.e., head of clinical development, head of clinical sciences, and group lead biostatistics) were involved in the DMC meeting for BSSR.

Safety

None.

3.4. Discussion on biosimilarity

Quality

The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its RMP. Overall, the conclusion that DRL_RI, RP, and RMP are similar is agreed. Regarding the observed differences the Applicant expanded the discussion but mainly stressed the fact that the differences are not clinically meaningful as the comparable efficacy, PD, safety, and immunogenicity in patients with moderate-to-severe rheumatoid arthritis in RI-01-003 Phase I clinical study was observed and in the RI-01-006 Phase III clinical study in low tumor burden follicular lymphoma patients efficacy equivalence between DRL_RI and MabThera was demonstrated and safety profile was comparable to that of MabThera.

Overall, taking into account the totality of the data provided, biosimilarity of Ituxredi with MabThera is considered demonstrated from a quality point of view.

Non-Clinical

Comparative toxicokinetic evaluation was performed following once weekly intravenous (infusion) administration in the Cynomolgus monkey over a 4-week dosing period. The data indicate that toxicokinetic parameters of Ituxredi, RMP and RP are comparable.

Clinical

Pharmacology

Based on the clinical studies conducted, the PK/PD clinical programme is sufficient. The results suggest that Ituxredi can be considered a biosimilar to MabThera.

Efficacy

The pivotal efficacy study was performed in LTB-FL, which – although not an approved indication of MabThera – is considered sensitive for detecting potential differences between the biosimilar DRL_RI and the reference medicinal product MabThera, as rituximab was administered as monotherapy and the comparability exercise was not confounded by concomitant treatment as well as advanced disease. The choice of model was also supported by CHMP (EMA/CHMP/SAWP/720016/2017).

The primary efficacy endpoint was met and supported by additional analyses with results all well within the predefined equivalence margin. A full 52-week dataset was provided. The second clinical study was conducted in Rheumatoid Arthritis, allowing assessment of similarity of DRL_RI and MabThera in a different non-oncology indication. Although the study was not powered for comparison of efficacy, the outcomes support the conclusion of similarity between Ituxredi and MabThera.

Safety

A sufficiently large number of patients was treated with either DRL_RI or the originator product, MabThera, in the pivotal Phase 3 study. The overall study duration of 52 weeks is also considered adequate.

Overall, the submitted safety and immunogenicity data are considered supportive for demonstration of biosimilarity. There were no clinically relevant differences in the safety profile of Ituxredi and the reference product MabThera identified. In general, the frequencies and nature of the adverse events were similar between Itruxedi and MabThera.

The complete final CSR with the full safety and immunogenicity data set has been submitted by the applicant and is considered supportive for further substantiation of similarity between Ituxredi and MabThera.

3.5. Extrapolation of safety and efficacy

Extrapolation of equivalence has to be made from the clinical studies in RA and LTB-FL to the MabThera-approved indications NHL (higher grade than LTB-FL), CLL and the auto-immune disorder ANCA-vasculitis (GPA and MPA) as well as PV. Extrapolation of safety and efficacy to all indications the applicant applied for, is acceptable as biosimilarity was demonstrated.

3.6. Additional considerations

None.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ituxredi is considered biosimilar to the reference product MabThera. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ituxredi is favourable in the following indications:

Non-Hodgkin's lymphoma (NHL)

Ituxredi is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Ituxredi maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy.

Ituxredi monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Ituxredi is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Ituxredi in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

Chronic lymphocytic leukaemia (CLL)

Ituxredi in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Ituxredi or patients refractory to previous Ituxredi plus chemotherapy.

Rheumatoid arthritis

Ituxredi in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Ituxredi has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and microscopic polyangiitis

Ituxredi, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Ituxredi, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

Pemphigus vulgaris

Ituxredi is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Non-oncology indications:

The MAH must ensure that all physicians who are expected to prescribe rituximab are provided with the following:

Product information
Physician information
Patient information
Patient Alert card

The Physician information about rituximab should contain the following key elements:

- The need for close supervision during administration in an environment where fullresuscitation facilities are immediately available
- The need to check, prior to rituximab treatment, for infections, for immunosuppression, forprior/current medication affecting the immune system and recent history of, or planned, vaccination
- The need to monitor patients for infections, especially PML, during and after rituximab treatment
- Detailed information on the risk of PML, the need for timely diagnosis of PML andappropriate measures to diagnose PML

- The need to advise patients on the risk of infections and PML, including the symptoms to beaware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The Patient information about rituximab should contain the following key elements:
- Detailed information on the risk of infections and PML
- Information on the signs and symptoms of infections, especially PML, and the need tocontact their doctor immediately if they experience any
- The importance of sharing this information with their partner or caregiver
- Information on the Patient Alert Card

The Patient Alert Card for rituximab in non-oncology indications should contain the following key elements:
- The need to carry the card at all times and to show the card to all treating health careprofessionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur

The Physician information, Patient information and Patient Alert Card must be agreed with the National Competent Authorities prior to distribution.

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[i] Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol. 1999;17(4):1244-1253.

[ii] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059-3067.

[iii] Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-1209.