CT-P10

A PROPOSED BIOSIMILAR TO RITUXAN®

FDA ADVISORY COMMITTEE MEETING BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AUC	Analytical Ultracentrifugation
$AUC_{0\text{-day14}}$	Area Under the Serum Concentration-Time Curve from Time Zero to Day 14
$AUC_{0\text{-inf}}$	Area Under the Serum Concentration-Time Curve from Time Zero to Infinity
$AUC_{0\text{-last}}$	Area Under the Concentration-Time Curve from Time Zero to Time of Last Quantifiable Concentration
AUC_{tau}	Area Under the Concentration-Time Curve at Steady State
BLA	Biologics License Application
BPCI	Biologics Price Competition and Innovation
BPD	Biosimilar Product Development
℃	Celsius
CD	Circular Dichroism
CD20	Cluster of Differentiation 20
CDC	Complement-Dependent Cytotoxicity
CE	Capillary Electrophoresis
CELISA	Cell-Based Enzyme-Linked Immunosorbent Assay
CHO	Chinese Hamster Ovary
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CI	Confidence Interval
CL	Clearance
CL_{ss}	Clearance at steady state
CLL	Chronic Lymphocytic Leukemia
$C_{av,ss}$	Average observed plasma concentration at steady state
C_{max}	Maximum Serum Concentration
$C_{max,ss}$	Maximum Serum Concentration at Steady State
C_{trough}	Trough serum concentration
$C_{trough,ss}$	Trough serum concentration at steady state
CQA	Critical Quality Attribute
CR	Complete Response
CRP	C-Reactive Protein
CRu	Unconfirmed Complete Response

CT	Computed Tomography
CVP	Cyclophosphamide, Vincristine, and Prednisone
DAS28	Disease Activity Score using 28 Joint Counts
DC	Dendritic Cell
DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid
DSC	Differential Scanning Calorimetry
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme Linked Immunosorbent Assay
EM	Equivalence Margin
EMA	European Medicines Agency
EOT	End of Treatment
ESI	Electrospray Ionization
ESR	Erythrocyte Sedimentation Rate
EU	European Union
Fab	Fragment Antigen Binding
FACS	Fluorescence-Activated Cell Sorting
Fc	Fragment Crystallizable
FcγR	Fc Gamma Receptors
FDA	Food and Drug Administration
FL	Follicular Lymphoma
FTIR	Fourier Transform Infra-Red
GELF	Groupe d'Etudes des Lymphomes Folliculaires
GMP	Good Manufacturing Practices
GPA	Granulomatosis with Polyangiitis
H + L	Heavy and Light Chains
HBV	Hepatitis B Virus
HC	Heavy Chain
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMW	High Molecular Weight
HPAEC-PAD	High Performance Anion Exchange with Pulsed Amperometric Detection
HPLC	High-Performance Liquid Chromatography
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEC	Ion Exchange Chromatography
IEF	Isoelectric Focusing
Ig	Immunoglobulin

IRR	Infusion-Related Reaction
ITT	Intent-to-Treat
IV	Intravenous
IWG	International Working Group
kDa	Kilo Daltons
λ_z	Terminal elimination rate constant
LC	Light Chain
LC-MS	Liquid Chromatography-Mass Spectrometry
LLoQ	Lower Limit of Quantification
LMW	Low Molecular Weight
LOCF	Last Observation Carried Forward
LS	Least Squares
LTBFL	Low Tumor Burden Follicular Lymphoma
MAC	Membrane Attack Complex
MALS	Multi-Angle Light Scattering
Man5	Mannose-5 Glycan
MFI	Micro-Flow Imaging
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MPA	Microscopic Polyangiitis
MRT	Mean Residence Time
MTX	Methotrexate
MW	Molecular Weight
NAb	Neutralizing Anti-Drug Antibody
NaCl	Sodium Chloride
NANA	N-Acetylneuraminic Acid
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not Estimable
NFAT	Nuclear Factor of Activated T-Cell
NGHC	Non-Glycosylated Heavy Chain
NHL	Non-Hodgkin’s Lymphoma
NK Cell	Natural Killer Cell
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PFS	Progression Free Survival

PHS	Public Health Service
pI	Isoelectric Point
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PNGase F	Peptide: N-Glycosidase F
PP	Per-Protocol
PR	Partial Response
PT	Preferred Term
PTF_{ss}	Peak to trough fluctuation ratio at steady state
PTM	Post-Translational Modification
PV	Pemphigus Vulgaris
QoL	Quality of Life
RA	Rheumatoid Arthritis
R-CVP	Rituximab, Cyclophosphamide, Vincristine, and Prednisone
RF	Rheumatoid Factor
RH	Relative Humidity
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SDS	Sodium-dodecyl Sulfate
SEC	Size Exclusion Chromatography
SPR	Surface Plasmon Resonance
SVP	Sub-Visible Particles
$T_{1/2}$	Terminal Elimination Half-Life
TK	Toxicokinetics
TLS	Tumor Lysis Syndrome
T_{max}	Time to Peak Concentration
$T_{max,ss}$	Time to maximum serum concentration at steady state
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitors
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
UV	Ultraviolet
UV_{280}	Ultraviolet Absorbance at 280 nm
V_d	Volume of Distribution
V_{ss}	Volume of distribution at steady state
VAS	Visual Analogue Scale

1 EXECUTIVE SUMMARY

1.1 Introduction

CELLTRION Inc. has developed CT-P10, a proposed biosimilar to United States (US)-licensed Rituxan® (rituximab; Biogen Inc. and Genentech, Inc., marketed in the European Union [EU] with the brand name MabThera®), and is seeking marketing approval following the regulatory pathway provided under Section 351(k) of the Public Health Service Act. This briefing document provides a summary of the evidence that supports licensure of CT-P10 as a biosimilar to Rituxan®.

Rituxan® contains rituximab, which is a cluster of differentiation 20 (CD20)-directed antibody. Rituxan® has been licensed since 1997 for use in the following oncologic and chronic inflammatory conditions (Rituxan® USPI, 2018):

- Non-Hodgkin's Lymphoma (NHL)
    - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent
    - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan® in combination with chemotherapy, as single-agent maintenance therapy
    - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
    - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL)
    - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately- to severely-active RA who have inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids
- Moderate to severe Pemphigus Vulgaris (PV) in adult patients[1]

In all licensed indications, Rituxan® binds to CD20 expressed on the surface of B-cells at all intermediate stages of differentiation, which leads to their elimination, reducing tumor burden and ameliorating B-cell mediated inflammatory events.

[1] This indication is protected by orphan drug exclusivity until June 07, 2025.

The Food and Drug Administration (FDA) guidance indicates that a biosimilar applicant may obtain licensure for fewer than all conditions of use for which the reference product is licensed (FDA, 2015; FDA, 2018). Due to the current intellectual property and exclusivity landscape, CELLTRION seeks licensure of CT-P10 for the Proposed Indications only. These are the indications presented in the draft label submitted in the May 29, 2018 351(k) biologic license application (BLA) resubmission. These three NHL indications ("Proposed Indications"[2]) are identical to the respective NHL indications in Rituxan® USPI (2018):

- Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to CT-P10 in combination chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy

Interchangeability of CT-P10 with the reference product is not proposed in CELLTRION's BLA.

The development program for CT-P10 has followed a stepwise approach, in line with the FDA guidance and EU guidelines for biosimilar biological products. CT-P10 has been demonstrated to be highly similar to Rituxan®[3] and MabThera®[3] in physicochemical structure, biological function, clinical pharmacology, and clinical efficacy and safety. Accompanied by a rigorous scientific justification for extrapolation to non-studied indications, the totality of data supports the approval of CT-P10 as a biosimilar for the Proposed Indications.

CELLTRION has fulfilled all statutory requirements for demonstrating biosimilarity of CT-P10 to Rituxan® based on the following evaluations:

- Comprehensive state-of-the-art analytical studies comparing CT-P10, Rituxan® and MabThera® demonstrated that CT-P10 is highly similar to Rituxan® in physicochemical and structural attributes (Section 3.2.1).
- An extensive range of *in vitro* functional assays relevant to mechanisms of action (MoA) was conducted to evaluate the biological and functional activities. CD20 binding and CD20-dependent activities including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), apoptosis and other activities confirmed that CT-P10 is highly similar to Rituxan®, having a similar effect on B-cells in these assays. The high similarity in biological and functional assays also address any potential residual uncertainty arising from minor differences observed in physicochemical and structural studies (Section 3.2.2).

[2] Throughout the remainder of this document, these three NHL indications – and no other indications – will be referred to as the Proposed Indications.

[3] Throughout the remainder of this document, US-licensed Rituxan® and EU-approved MabThera® will be referred to as Rituxan® and MabThera®, respectively.

- The 3-way comparative analytical studies also demonstrated highly similar physicochemical structure and function between CT-P10, Rituxan® and MabThera®, thereby establishing a scientific bridge between the US-licensed Rituxan® reference product and the EU-approved MabThera® comparator product.
- Non-clinical studies comparing CT-P10 and MabThera® indicated similar tissue cross-reactivity *in vitro* and similar *in vivo* pharmacokinetic (PK) and toxicity profiles for these products and, by extension, the similarity would extend to Rituxan® (Section 4).
- The clinical pharmacology assessments in follicular lymphoma (FL) patients demonstrated similar PK and pharmacodynamics (PD) between CT-P10 and Rituxan® (Section 5.2).
- Comparative clinical efficacy and safety studies in FL patients demonstrated therapeutic equivalence between CT-P10 and Rituxan® and showed similar immunogenicity and comparable safety profiles for CT-P10 and Rituxan® (Section 5.3 and Section 5.4).
- Comparative PK and immunogenicity assessments in patients with rheumatoid arthritis (RA) demonstrated similar PK and immunogenicity across CT-P10, Rituxan® and MabThera® (Sections 5.2.1.3, 5.4.2.3 and 5.4.2.4).

The collective results from analytical, non-clinical and clinical studies show that CT-P10 is highly similar to Rituxan® and that there are no clinically meaningful differences between CT-P10 and Rituxan® in terms of the safety, purity and potency of the product. As such, the totality of evidence supports the approval of CT-P10 as a biosimilar to Rituxan® for the Proposed Indications (Section 1.1).

The analytical, non-clinical, and clinical studies are intended solely to satisfy the statutory requirements for the licensure of a biosimilar and are not intended to encourage the use of CT-P10 in any indication not included in CELLTRION's draft label submitted with its May 29, 2018 351(k) BLA resubmission.

1.2 Regulatory Background

The Biologics Price Competition and Innovation (BPCI) Act of 2009 created an abbreviated licensure pathway for biological products shown to be "biosimilar" to an FDA-licensed biological product. This pathway enables a biosimilar product to be licensed based on less than a full complement of product-specific non-clinical and clinical data by relying on the established safety and effectiveness of the reference product. The basis for an abbreviated biosimilar development program is that a molecule shown to be structurally and functionally highly similar to a reference product can be expected to behave like the reference product in the clinical setting.

The Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product" (BPCI Act).

The FDA guidance recommends a stepwise approach to demonstrate biosimilarity, which emphasizes structural and functional characterization of the proposed biosimilar product and the reference product as the foundation of biosimilarity. Based on a demonstration of analytical similarity, targeted non-clinical, clinical pharmacology, and clinical efficacy and safety studies from the subsequent steps of the development plan are designed to address any residual uncertainties in biosimilarity observed at the previous steps. The determination of biosimilarity is based on the "totality of evidence" from the stepwise development studies.

CELLTRION originally filed a BLA (BLA #761088) for marketing authorization of CT-P10, a proposed biosimilar to Rituxan®, under Section 351(k) of the Public Health Service Act in April 2017. In response to a Complete Response Letter issued in February 2018, CELLTRION resubmitted the BLA in May 2018 with additional long-term efficacy and safety data from Study CT-P10 3.3 (in advanced FL) generated since the initial submission and new clinical data from Study CT-P10 3.4 (in low tumor burden follicular lymphoma [LTBFL]). The Advisory Committee has been convened to provide guidance to the FDA on the evidence supporting the biosimilarity of CT-P10 to Rituxan®.

1.3 Overview of CT-P10 Development Program

In accordance with the stepwise approach, the CT-P10 biosimilar development program included extensive comparative analytical studies followed by specifically selected non-clinical and clinical studies (Figure 1). CELLTRION has had several discussions with the FDA and received input from the FDA regarding the CT-P10 development program.

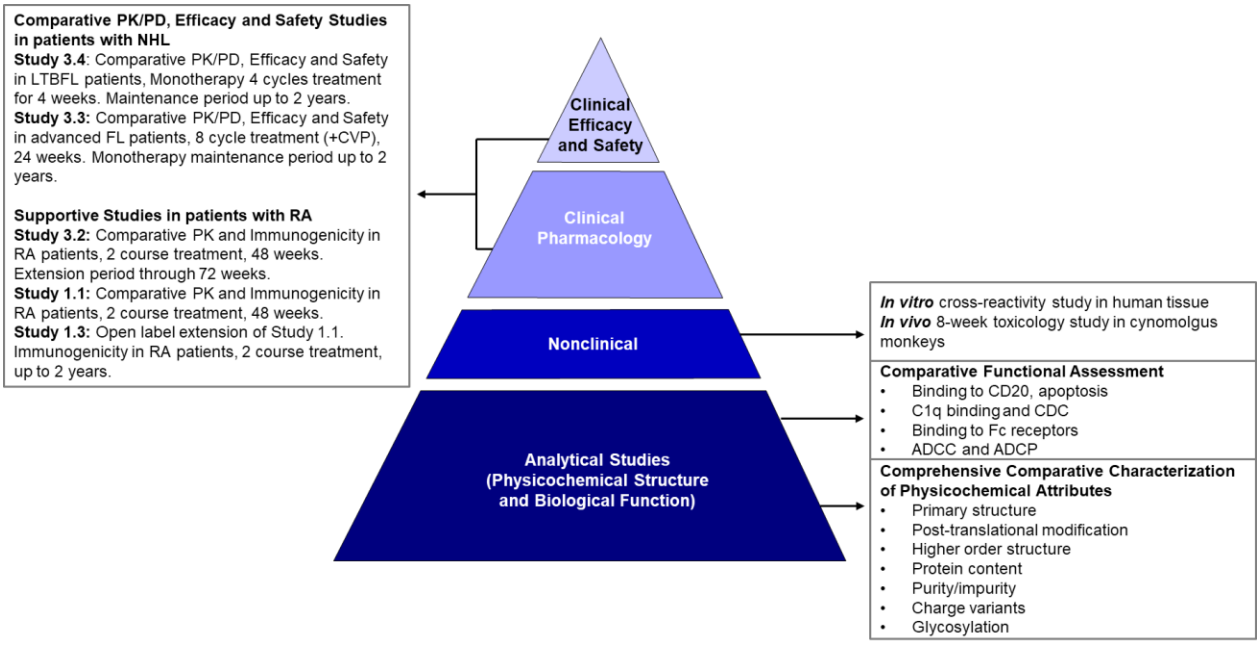


Figure 1: Stepwise Approach to Establish Biosimilarity (Totality of Evidence)

The first step of the CT-P10 similarity assessment was analytical characterization of the structure and physicochemical properties of CT-P10, Rituxan® and MabThera® using an array of orthogonal, state-of-the-art techniques. Comprehensive overviews of the results of physicochemical and structural studies are provided in Section 3.2.1. Next, the biological and functional activities of CT-P10, Rituxan® and MabThera® were compared using a number of assays measuring CD20 binding, interaction with Fc receptors and complement, and assays measuring the impact of the products on B-cells, as discussed in Section 3.2.2.

Based on the results of the comprehensive analytical studies, 2 non-clinical studies were conducted: a tissue immunohistochemistry study and a comparative toxicity study in cynomolgus monkeys (Section 4).

Finally, clinical assessments were conducted to confirm the similarity of CT-P10 and the reference products. These included 5 comparative PK/PD, efficacy, safety and immunogenicity studies, 2 in patients with FL and 3 in patients with RA (Table 2).

1.4 Rituximab in Treatment of NHL

Rituxan® was first approved by the FDA in 1997, and has been used worldwide to treat over 4.4 million patients with B-cell malignancies (e.g., NHL and CLL) (Genentech, Inc., 2017), and chronic inflammatory conditions. According to the National Comprehensive Cancer Network (NCCN) guidelines (2018), treatment with rituximab, as monotherapy or in combination with chemotherapy, is standard of care for patients with B-cell malignancies. Such treatment is associated with prolonged progression-free survival (PFS) and overall survival (OS) in several indications (Eichhorst *et al*., 2015; Sehn *et al*., 2005; Molina *et al*., 2008; Vidal *et al*., 2011). An estimated 75,000 patients in the US will be diagnosed with NHL in 2018 according to statistics presented by the National Cancer Institute (NCI).

Patient access to biologic treatments like rituximab may be limited by cost. Along with other biologic treatments, rituximab therapy represents a significant cost burden to the healthcare system. The introduction of biosimilar treatments like CT-P10 is hoped to increase competition and improve overall access to biologic treatments.

1.5 Structural and Functional Similarity to Reference Product

Structural similarity studies included extensive comparative analyses of CT-P10, Rituxan® and MabThera® in primary structure, higher order structure, post-translational modifications, content, charge variants, purity and impurity profiles, and glycan profiles generally using 12-15 lots of each product. Functional similarity evaluations comprised multiple models that assessed all known and putative biological pathways of the MoA of rituximab. Statistical analyses of the data from studies of both physicochemical structure and function were conducted using the tiered approach with pre-specified criteria, as recommended by the FDA. Full details of the statistical analysis are provided in Section 3.1.

Table 1 provides a summary of the conclusions of statistical analysis of data from structural and functional similarity studies. While the majority of physicochemical techniques demonstrated

identical or highly similar properties between CT-P10, Rituxan® and MabThera®, minor differences in levels of size variants, charge variants, and individual glycan species were detected, as indicated in Table 1. Importantly, these differences were very small, had no impact on biological activities in functional similarity studies, and were considered highly unlikely to have any impact on the efficacy, safety or immunogenicity of CT-P10, as were confirmed by subsequent clinical studies.

Table 1: Summary of Analytical Similarity Assessment

Attribute	Analytical Test	CT-P10 vs. Rituxan® Highly Similar	MabThera® vs. Rituxan® Highly Similar	CT-P10 vs. MabThera® Highly Similar
Physicochemical and Structural Attributes				
Primary Structure	Peptide mapping (HPLC)	✓	✓	✓
	Amino acid analysis	✓	✓	✓
	Molar absorptivity	✓	✓	✓
	N-terminal sequencing	✓	✓	✓
	C-terminal sequencing	✓	✓	✓
	Intact mass (LC-MS)	✓	✓	✓
Post-translational Modifications	Peptide mapping (LC-MS)			
	- Deamidation	<0.1% higher Asn365[1] and <0.3% lower Asn388[1]	<0.1% higher Asn365[1]	<0.4% lower Asn388[1]
	- Oxidation	✓	✓	✓
	- N-terminal glutamine variants	✓	✓	✓
	- C-terminal lysine variants	✓	✓	✓
Higher Order Structure	FTIR	✓	✓	✓
	DSC	✓	✓	✓
	CD	✓	✓	✓
	Free thiol content	✓	✓	✓
	Disulfide bonding	✓	✓	✓
Content	Protein concentration	✓	✓	✓
	Extractable volume	✓	✓	Not tested
Purity/Impurity	SEC-HPLC	<0.5% higher monomer[1], <0.6% lower HMW[1], <0.04% higher LMW[1]	✓	<0.3% higher monomer[1], <0.4% lower HMW[1], <0.06% higher LMW[1]
	SEC-MALS	✓	✓	✓
	AUC	✓	✓	✓
	Non-reduced CE-SDS	<2.4% higher Intact IgG[1]	✓	✓
	Reduced CE-SDS	<0.4% higher NGHC[1] <0.4% lower H+L[1]	✓	<0.4% higher NGHC[1] <0.4% lower H+L[1]
	Residual Host Cell Protein	✓	✓	✓
	Residual Host Cell DNA	✓	✓	✓
	Residual rProtein A	✓	✓	✓
	SVP by MFI	✓	✓	✓
	SVP by Light obscuration	✓	✓	✓

Attribute	Analytical Test	CT-P10 vs. Rituxan® Highly Similar	MabThera® vs. Rituxan® Highly Similar	CT-P10 vs. MabThera® Highly Similar
Charge Variants	IEF	✓	✓	✓
	IEC-HPLC			
	- Acidic forms	<4.5% lower levels[1]	✓	<4.3% lower levels[1]
	- Main and basic forms	✓	✓	✓
Glycosylation	Oligosaccharide profiling	<1.5% higher Man5[1] <1.1% higher G0+Man5[1]	✓	<1.6% higher Man5[1] <1.2% higher G0+Man5[1]
	N-linked glycan analysis	<1.9% higher Man5[1] <1.5% higher G0+Man5[1]	✓	<1.9% higher Man5[1] <1.5% higher G0+Man5[1]
	Sialic acid analysis	✓	✓	✓
	Monosaccharide analysis	✓	✓	✓
	Glycation analysis	✓	✓	✓
Biological & Functional Activities				
Fab-Binding	Cell-based CD20 binding (CELISA)	✓	✓	✓
	Apoptosis using Raji cell (FACS)	✓	✓	✓
Fc-Binding	C1q binding	✓	✓	✓
	FcγRIIIa-V binding affinity (SPR)	✓	✓	✓
	FcγRIIIa-F binding affinity (SPR)	✓	✓	✓
	FcγRIIIb binding affinity (SPR)	✓	✓	✓
	FcγRIIa binding affinity (SPR)	✓	✓	✓
	FcγRIIb binding affinity (SPR)	✓	✓	✓
	FcγRI binding affinity (SPR)	✓	✓	✓
	FcRn binding affinity (SPR)	✓	✓	✓
Fab-Fc-mediated Activities	CDC using WIL2-S cell	✓ (Within EM[2])	✓ (Within EM[2])	✓ (Within EM[2])
	ADCC using PBMC (FcγIIIa-V/F)	✓ (Within EM[2])	✓ (Within EM[2])	✓ (Within EM[2])
	ADCC using reporter assay (FcγIIIa-V)	✓	✓	✓
	ADCP using Raji cell	✓	✓	✓

✓ Indicates that the product met the relevant statistical acceptance criteria for high similarity described in Section 3.1.

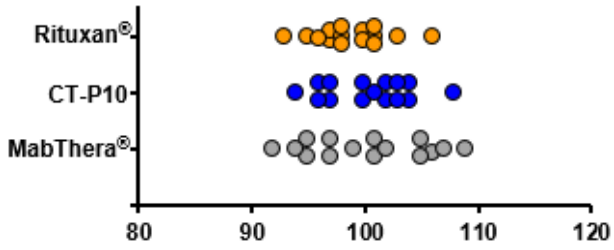
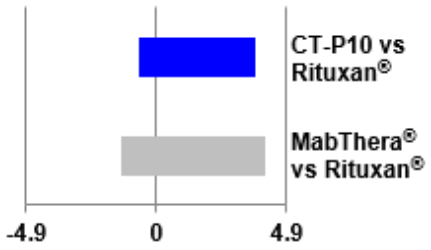
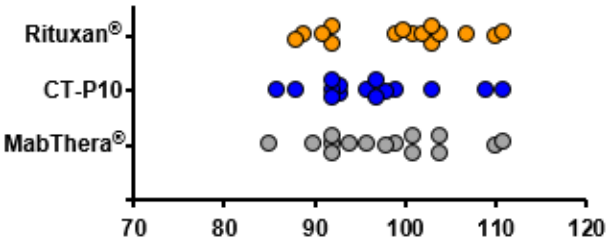
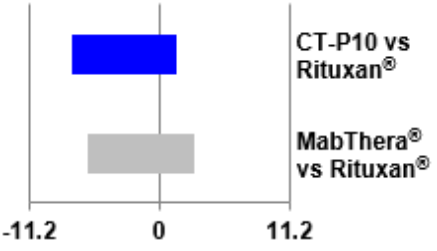
[1] Numbers are the difference in mean values of the products. The numbers are given for CT-P10 compared to Rituxan®, MabThera® compared to Rituxan® and CT-P10 compared to MabThera®. Differences detected in statistical analysis had no impact on biological activities in similarity studies.

[2] Equivalent, per pre-specified statistical analysis.

Statistical analyses of data from biological and functional assays confirmed that CT-P10, Rituxan® and MabThera® are highly similar. Figure 2 shows the data demonstrating high similarity of CT-P10, Rituxan® and MabThera® in CDC and ADCC, key functional activities of rituximab.

In addition, no differences between the products were detected in assays using B-cells from individuals of different disease state, further supporting that CT-P10 can be expected to have the same therapeutic effect as Rituxan® in the Proposed Indications (Section 1.1).

Comprehensive overviews of the results from physicochemical and functional similarity studies are provided in Section 3.2.1 and Section 3.2.2, respectively.

	Lot Data Points (%, Relative Values)	Equivalence Test (90% CI)
CDC WIL2-S target cells		
ADCC Raji target cells, FcγRIIIa-V/F PBMC effector cells (0.035 µg/mL)		

Notes: Relative activity was determined against CT-P10 *in-house* reference standard.
Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.
The 90% CI of the mean difference between the 2 products (blue or grey bars) was required to be within the equivalence margin (±1.5 σ_R of Rituxan® lots, grey lines) to meet the equivalence acceptance criteria.

Figure 2: CDC (EC_{50}) and ADCC (Cytotoxicity) of Rituxan®, CT-P10 and MabThera® and Equivalence Test Results

In conclusion, the results of the 3-way similarity studies demonstrate that CT-P10, Rituxan® and MabThera® are highly similar in physicochemical structure and in all biological activities associated with known and putative biological functions and therapeutic effects. Thus, these studies demonstrate similarity of CT-P10 to the US reference product and provide an analytic bridge between Rituxan® and MabThera®, supporting the use of MabThera® in non-clinical studies.

Based on these data, CT-P10 and Rituxan® can be expected to have similar therapeutic effects in the Proposed Indications (Section 1.1).

1.6 Key CT-P10 Clinical Studies for Demonstration of Similarity

The CT-P10 clinical program was developed in consultation with the FDA and the European Medicines Agency (EMA) to support the global development of the product and included 924 subjects across 5 studies and specifically 398 patients with FL. Low tumor burden follicular lymphoma (LTBFL) was recommended by the FDA as the most sensitive and homogenous setting for the assessment of comparative efficacy, safety and immunogenicity. Studies in advanced follicular lymphoma (FL) and Rheumatoid Arthritis (RA) were recommended by the EMA. In addition, the studies in RA patients were required to support clinical similarity of CT-P10 and Rituxan® in terms of PK and immunogenicity. The advice provided by the FDA and the EMA has been systematically integrated into the clinical development program.

The key clinical trials supporting CT-P10 are described in Table 2. The clinical similarity evaluation focused on the data from FL patients, with additional PK and immunogenicity data obtained from studies in patients with RA.

Study CT-P10 3.4 in patients with LTBFL and Study CT-P10 3.3 in patients with advanced FL were designed to compare efficacy and safety between CT-P10 and Rituxan®, and are currently ongoing. For Study CT-P10 3.4, the primary efficacy endpoint and PK, PD, safety and immunogenicity data over 7 months for each patient are available. For Study CT-P10 3.3, primary endpoint results (i.e., PK at Cycle 4 and efficacy over 8 cycles) and additional efficacy and safety data during the monotherapy maintenance period (with a median follow-up duration of 22.6 months) are available. Both studies in FL patients compared CT-P10 versus US-licensed Rituxan®.

Studies CT-P10 3.2, CT-P10 1.1, and CT-P10 1.3 in RA patients have been completed. Study CT-P10 3.2 compared CT-P10, EU-approved MabThera® and US-licensed Rituxan® and generated PK similarity and immunogenicity data in RA patients. In addition, Study CT-P10 3.2 provided immunogenicity data following a single transition from Rituxan® and MabThera® to CT-P10. Studies CT-P10 1.1 and 1.3 were conducted using MabThera® as a comparator and served for the EU approval of CT-P10. As clinical similarity between CT-P10 and Rituxan is primarily supported by the studies in FL patients, only PK similarity and immunogenicity results from RA studies are discussed.

Table 2: Summary of Key CT-P10 Clinical Studies

	Study CT-P10 3.4 (Therapeutic Equivalence)	**Study CT-P10 3.3** (PK Similarity/ Therapeutic Non-inferiority)	**Study CT-P10 3.2** (3-way PK Similarity/Therapeutic Equivalence)	**Study CT-P10 1.1** (PK Similarity)	**Study CT-P10 1.3** (Extension Study of CT-P10 1.1)
Subjects	Patient with LTBFL (N=258)	Patients with Advanced FL (N=140)	Patients with RA (N=372)	Patients with RA (N=154*)	Patients with RA (N=87[#])
Study Design	Phase 3, randomized (1:1), controlled, multicenter, 2-arm, double-blind	Phase 1/3 randomized (1:1), controlled, multicenter, 2-arm, double-blind	Phase 3 randomized, controlled, multicenter, 3-arm, double-blind	Phase 1 randomized (2:1), controlled, multicenter, 2-arm, double-blind	Open-label, single-arm, maintenance
Reference Product / Comparator	Rituxan®	Rituxan®	Rituxan® and MabThera®	MabThera®	-
Doses	Induction: 375 mg/m^2 as an IV infusion given every week for 4 weeks. Maintenance: 375 mg/m^2 as an IV infusion given every 2 months up to 12 cycles (up to 6 cycles of randomized product followed by up to 6 cycles of CT-P10).	Induction: 375 mg/m^2 as an IV infusion given every 3 weeks in combination with chemotherapy, for up to 8 cycles. Maintenance: 375 mg/m^2 as an IV infusion given every 2 months up to 12 cycles.	Two 1,000 mg IV infusions separated by 2 weeks (one course) every 24 weeks up to 3 courses.	Two 1,000 mg IV infusions separated by 2 weeks (one course) every 24 weeks up to 2 courses.	Two 1,000 mg IV infusions separated by 2 weeks (one course) every 24 weeks up to 2 courses.
Background Therapy	None	Induction: Cyclophosphamide (750mg/m^2) IV on 1st day of each cycle, vincristine (1.4 mg/m^2 [max 2 mg] on 1st day of each cycle) and prednisone orally 40 mg/m^2 on Days 1-5 of each cycle (CVP)	Methotrexate (7.5-25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week)	Methotrexate (10-25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week)	Methotrexate (10-25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week)

	Study CT-P10 3.4 (Therapeutic Equivalence)	**Study CT-P10 3.3** (PK Similarity/ Therapeutic Non-inferiority)	**Study CT-P10 3.2** (3-way PK Similarity/Therapeutic Equivalence)	**Study CT-P10 1.1** (PK Similarity)	**Study CT-P10 1.3** (Extension Study of CT-P10 1.1)
Premedication	Antipyretic, antihistamine and glucocorticoid administered 30 minutes before each infusion	Antipyretic, antihistamine and glucocorticoid administered 30 minutes before each infusion	Methylprednisolone, antipyretics and antihistamines 30 to 60 minutes prior to each infusion	Methylprednisolone, antipyretics and antihistamines 30 to 60 minutes prior to each infusion	Methylprednisolone, antipyretics and antihistamines 30 to 60 minutes prior to each infusion
Study Objectives	Therapeutic equivalence	PK similarity and efficacy non-inferiority	PK similarity, PK bridge, therapeutic equivalence, and single transition data (extension)	PK similarity	Long term efficacy, safety, immunogenicity data
Primary Endpoints	Efficacy: ORR (Complete Response [CR]+ unconfirmed Complete Response [CRu]+Partial response [PR]) over 7 months	PK: AUC_{tau}, $C_{max,ss}$ at Cycle 4 Efficacy: ORR (CR+CRu+PR) over 24 weeks	PK: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} over 24 weeks Efficacy: DAS28 (CRP) at Week 24	PK: $AUC_{0\text{-last}}$, C_{max} over 24 weeks	N/A
Other Endpoints	ORR during the study period, additional efficacy, PK, PD, safety, immunogenicity and biomarkers	Additional PK, PD, efficacy, safety, immunogenicity and biomarkers	Additional PK, efficacy, PD, safety immunogenicity and biomarkers	Additional PK, efficacy, PD, safety immunogenicity and biomarkers	Long-term efficacy, safety and immunogenicity
Study Duration	Induction period: 4 cycles (weekly, up to 4 weeks) Maintenance period: maximum 12 cycles (every 2 months, up to 2 years. Follow-up period: up to 27 months from Day 1 of Cycle 1 of the last patient.	Induction period: 8 cycles (3-weekly, up to 24 weeks) Maintenance period (monotherapy): maximum 12 cycles (every 2 months, up to 2 years) Follow-up period: up to 3 years from Day 1 of Cycle 1 of last patient	Main period: Week 0 through Week 48 Extension period (single transition): Week 48 through Week 72	Week 0 through Week 48	Up to 96 weeks including Study CT-P10 1.1

*1 Patient (CT-P10) who was randomized but did not receive the study drug was excluded from all analyses of Study CT-P10 1.1.
Patients were from Study CT-P10 1.1.
Abbreviations: $AUC_{0\text{-}inf}$, Area under the serum concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, Area under the concentration-time curve from time zero to time of last quantifiable concentration; AUC_{tau}, Area under the concentration-time curve at steady state; C_{max}, Maximum serum concentration; $C_{max,ss}$, Maximum serum concentration at steady state; CR, Complete response; CRP, C-Reactive Protein; CRu, Unconfirmed complete response; CVP, Cyclophosphamide, Vincristine, and Prednisone; DAS28, Disease Activity Score using 28 Joint Counts; FL, Follicular lymphoma; IV, Intravenous; LTBFL, Low tumor burden follicular lymphoma; N/A, Not applicable; ORR, Overall response rate; PD, Pharmacodynamics; PK, Pharmacokinetics; PR, Partial response; RA, Rheumatoid arthritis

1.6.1 Similarity Based on Clinical Pharmacology Data

The PK/PD profile of rituximab in NHL has been well studied and published. There are no covariates with prominent impact on PK (Rituxan® USPI, 2018). Therefore, there are no specific recommendations regarding rituximab dose adjustment across the Proposed Indications (Section 1.1). LTBFL, advanced FL and RA patient populations were considered as sufficiently sensitive for evaluating PK similarity between CT-P10 and Rituxan®.

PK Similarity

CT-P10 had a similar PK profile to Rituxan® as measured by area under the concentration-time curve (AUC) at steady state (AUC_{tau}) and maximum serum concentration at steady state ($C_{max,ss}$) during repeat dosing in patients with advanced FL (Figure 3). Supportive PK data obtained from Study CT-P10 3.4 in LTBFL patients also demonstrated similar serum concentrations for CT-P10 and Rituxan® over the 7-month assessment period.

PK similarity has been also shown between CT-P10 and Rituxan® or MabThera® by AUC from time zero to infinity ($AUC_{0\text{-}inf}$), AUC from time zero to time of last quantifiable concentration ($AUC_{0\text{-}last}$) and maximum serum concentration (C_{max}) in patients with RA (Figure 4). The PK similarity in RA patients is also supported by the additional key PK parameter, AUC from time zero to Day 14 ($AUC_{0\text{-}day14}$), which was requested by the FDA.

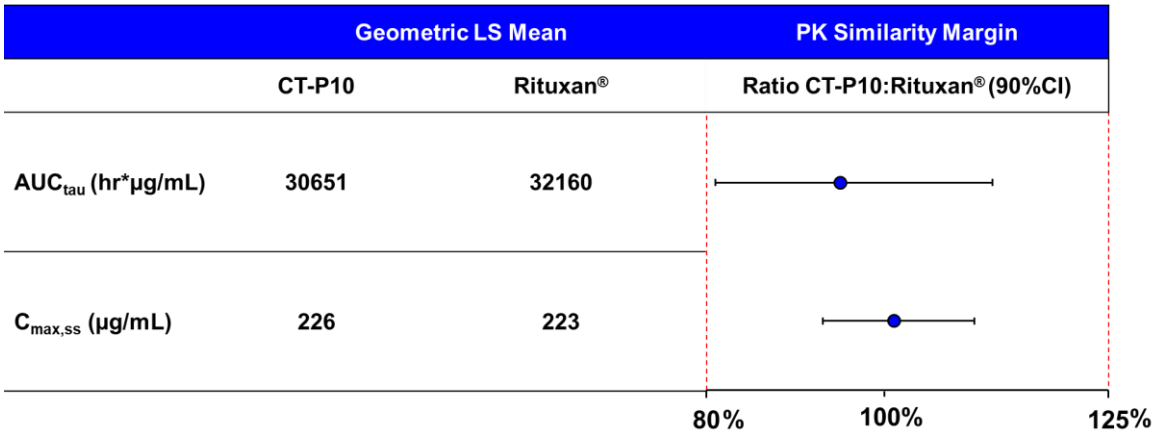


Figure 3: Primary PK Analysis of Study CT-P10 3.3

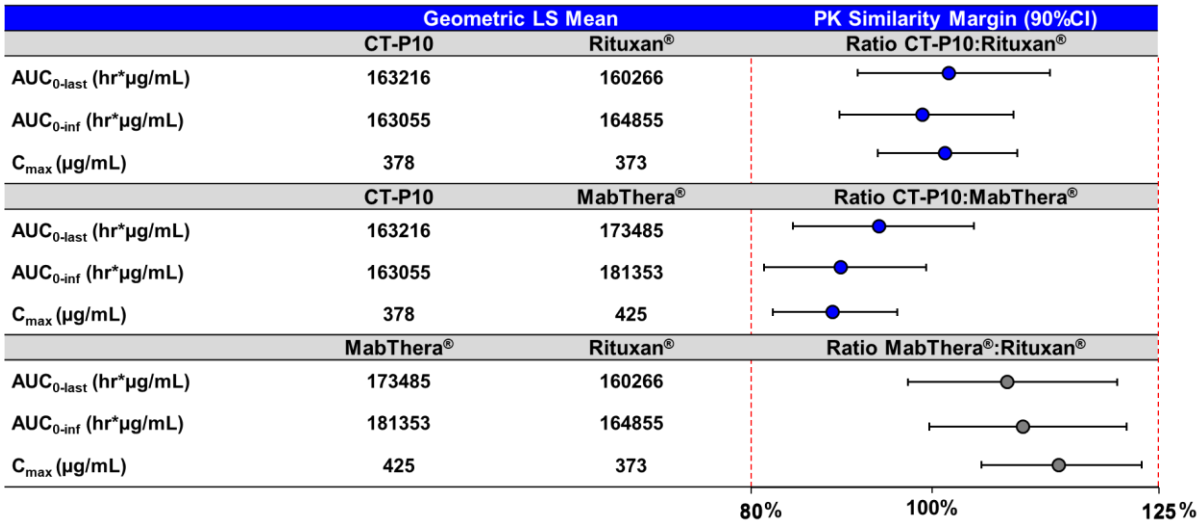
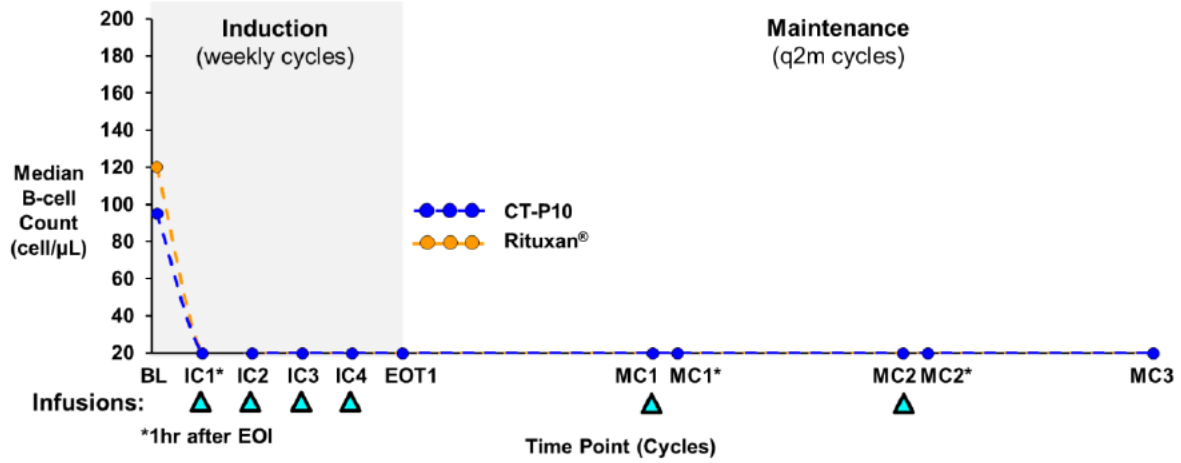


Figure 4: Primary PK Analysis of Study CT-P10 3.2

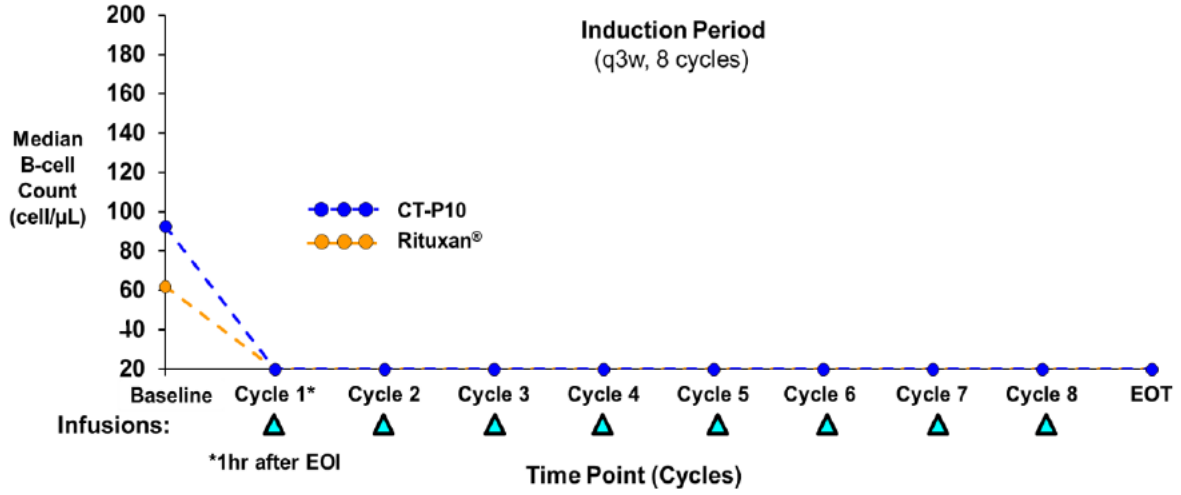
Similarity Based on PD

CT-P10 and Rituxan® displayed similar PD profiles in patients with FL based on the median decrease from baseline in B-cell counts (Figure 5 and Table 6).



Abbreviations: BL, Baseline; EOI, End of infusion; IC, Induction Cycle; MC, Maintenance Cycle; q2m, Every 2 months
Note: Any values below the lower limit of quantification (LLoQ) were set as LLoQ which was 20 cells/µL.

Figure 5: B-cell Depletion Profiles of CT-P10 and Rituxan® During Induction Period (Weekly, 4 Cycles) and Maintenance Period (Every 2 Months, 2 Cycles) over 7 Months of Intravenous 375 mg/m2 of CT-P10 and Rituxan® (Study CT-P10 3.4)



Abbreviation: EOI, End of infusion; EOT, End of treatment; q3w, Every 3 weeks
Note: Any values below the lower limit of quantification (LLoQ) were set as LLoQ which was 20 cells/µL.

Figure 6: B-cell Depletion Profiles During Induction Period with 8 Cycles of Intravenous 375 mg/m2 of CT-P10 and Rituxan® Administered on Background of CVP (Study CT-P10 3.3)

1.6.2 Comparative Clinical Efficacy Data

The choice of LTBFL patient population and the use of objective overall response as a primary endpoint were recommended by the FDA as the most sensitive tools to demonstrate that there

are no clinically meaningful differences between CT-P10 and Rituxan® in relation to efficacy. The choice of advanced FL patients for comparative efficacy evaluation was recommended by the EMA.

Comparative efficacy data for CT-P10 and Rituxan® were obtained in the following studies:

- Study CT-P10 3.4 in patients with LTBFL demonstrated the therapeutic equivalence of CT-P10 to Rituxan® according to the primary efficacy endpoint; the overall response rate (ORR) over 7 months was 83.1% in the CT-P10 group compared with 81.3% in the Rituxan® group (Figure 7). Based on an exact binomial test, the difference (90% exact confidence interval [CI]) in ORR between CT-P10 and Rituxan® was 1.8% (-6.43, 10.20), which was entirely within the equivalence margin of ±17%, as was agreed with the FDA. Consistent results were observed for the intent-to-treat (ITT) and per-protocol (PP) datasets and the sensitivity analyses using missing data imputation.

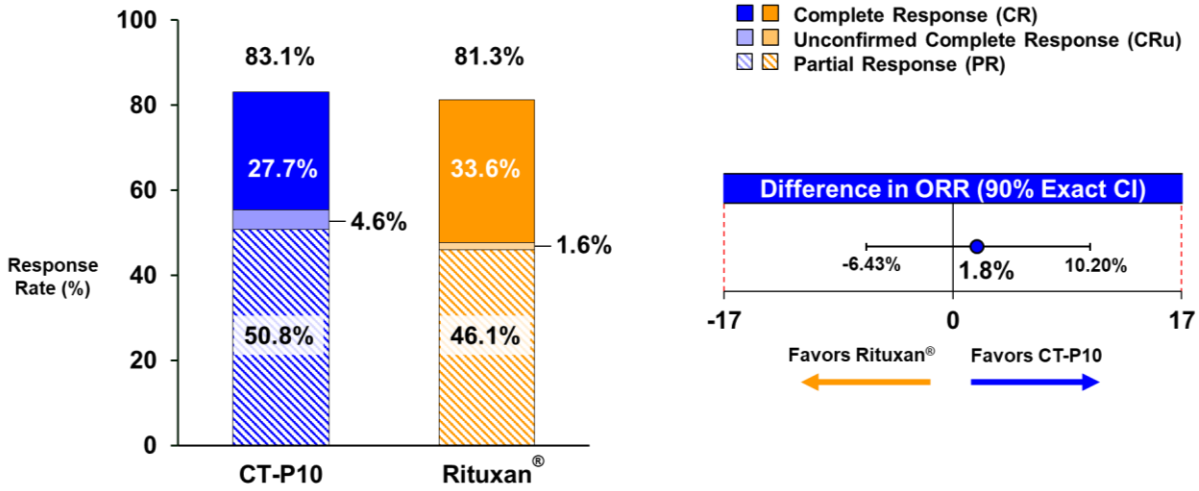


Figure 7: Difference in ORR Over 7 Months (Study CT-P10 3.4)

- Study CT-P10 3.3 in patients with advanced FL demonstrated that CT-P10 was non-inferior to Rituxan® according to the primary efficacy endpoint; the ORR over 8 cycles was 95.7% in the CT-P10 group compared with 90.0% in the Rituxan® group. The difference (lower bound of 95% CI) of the ORR between CT-P10 and Rituxan® was 5.7% (-3.4%) and lies on the positive side of the non-inferiority margin of -7%, which was based on a point estimate difference (Figure 8). In addition, the duration of responses, PFS and OS in the ongoing monotherapy maintenance period support the similarity between CT-P10 and Rituxan®.

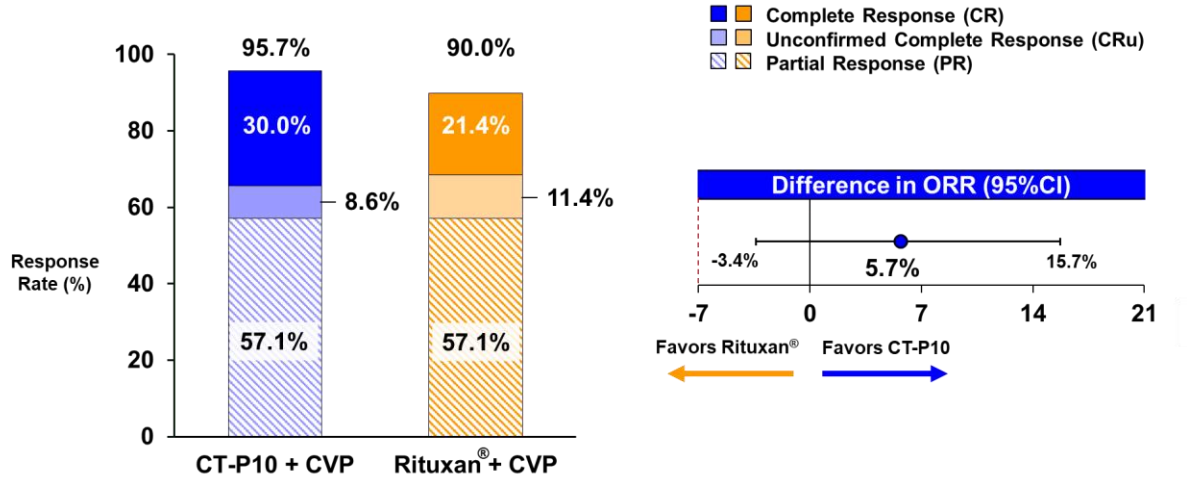
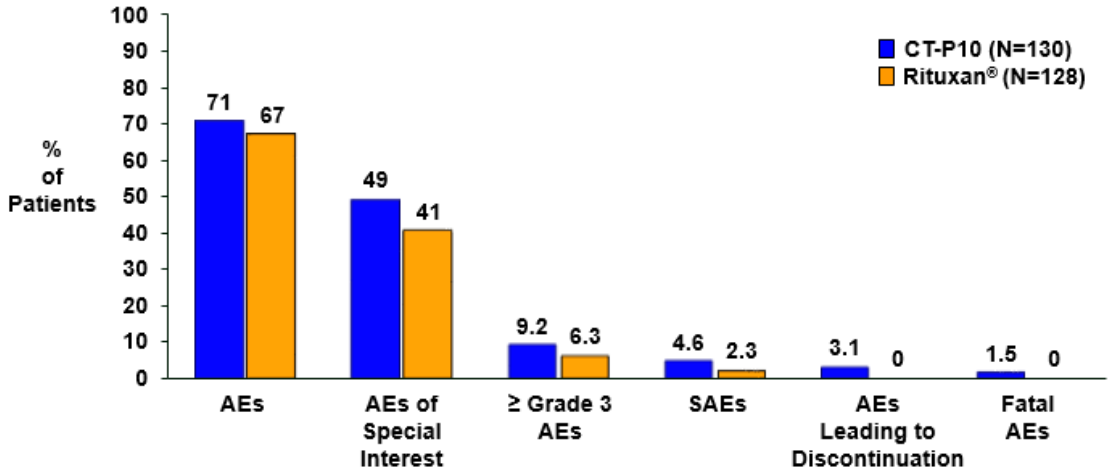


Figure 8: Difference in ORR over 8 Cycles (Study CT-P10 3.3)

1.6.3 Clinical Safety and Immunogenicity Data

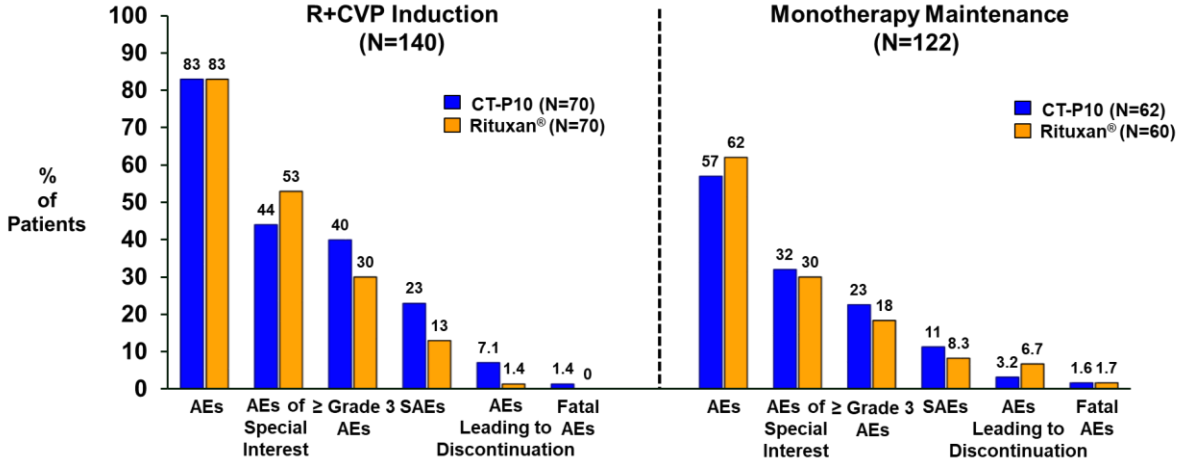
Eligibility criteria and safety assessments across all CT-P10 clinical studies were systematically developed, taking into account the safety features of Rituxan®/MabThera®, including label warnings/precautions, contraindications, and adverse events (AEs) outlined in the Rituxan® USPI (2018). Comprehensive comparative safety assessments were conducted across all clinical trials. Assessments included AEs, AEs leading to permanent study drug discontinuations, AEs of special interest (AESIs), clinical laboratory testing (including Human Immunodeficiency Virus [HIV], Hepatitis B Virus [HBV], Hepatitis C Virus [HCV], virology screening), and tuberculosis assessments, immunogenicity, vital signs, physical examinations, and electrocardiograms.

Comparable safety profiles between CT-P10 and Rituxan® were observed across CT-P10 FL trials comprising 258 patients with LTBFL and 140 patients with advanced FL; results were consistent with the well-known safety profile of Rituxan®. Across FL studies, the incidences of AEs, grade ≥3 AEs, serious adverse events (SAEs), AEs leading to permanent study drug discontinuation, and AESIs were comparable between CT-P10 and Rituxan® (Figure 9). Between CT-P10 and Rituxan®, the incidence, type, and severity of AEs were comparable. No new safety signals were identified, and the AEs observed were consistent with those described in the Rituxan® USPI (2018).



Note: Cut-off of 7 months assessment.

(a) LTBFL Study



Note: Median follow-up of 22.6 months on July 31, 2017 cut-off (including ≥ 10 months on monotherapy treatment).

(b) Advanced FL Study

Figure 9: Summary of Adverse Events in (a) LTBFL Study (Study CT-P10 3.4) and (b) Advanced FL Study (Study CT-P10 3.3)

Immunogenicity was evaluated using tiered state-of-the-art, validated methods. Results demonstrated similar anti-drug antibody (ADA) levels in 258 patients with LTBFL (over 7 months in Study CT-P10 3.4), 140 patients with advanced FL (during induction period and maintenance period, up to cut-off date of July 31, 2017 in Study CT-P10 3.3). Additional immunogenicity data was also generated in 525 patients with RA (up to 72 weeks in Study CT-P10 3.2 and up to 96 weeks in Studies CT-P10 1.1 and CT-P10 1.3). The proportion of patients who were ADA positive was comparable between the CT-P10 and Rituxan®/MabThera® groups, as were the very low incidence of neutralizing anti-drug antibody (NAb) positivity and the intensity of ADA titer. The effects of the presence of ADA on PK, efficacy and safety appeared to be comparable between CT-P10 and Rituxan®/MabThera® groups. Across the CT-P10 studies, no discernable differences in immunogenicity findings were identified between the 2 treatment groups.

1.7 Extrapolation across Indications

CELLTRION seeks licensure of CT-P10 for the Proposed Indications (Section 1.1). The rationale for seeking approval for those indications not specifically evaluated in the CT-P10 development program is based on an understanding that once biosimilarity is established through structural, functional, non-clinical and clinical studies, extrapolation can be made to other indications for which the reference product has been tested and approved. Extrapolation is scientifically justified based on a) high similarity in molecular structure; b) high similarity in biological activities including CD20 binding that is relevant to efficacy in NHL indications; c) a common MoA that is central to NHL indications; d) well studied PK/PD across NHL indications; and e) a comparable safety and immunogenicity profile across NHL indications notwithstanding the differences relating to use of background chemotherapy.

The data from analytical, non-clinical and clinical studies show that CT-P10 is highly similar to Rituxan® and that there are no clinically meaningful differences between CT-P10 and Rituxan® in terms of safety, purity and potency. As such, the totality of evidence supports the approval of CT-P10 for the Proposed Indications (Section 1.1).

2 BACKGROUND INFORMATION

2.1 Regulatory Pathway

CELLTRION originally filed a BLA (BLA #761088) for marketing authorization of CT-P10, a proposed biosimilar to Rituxan®, under Section 351(k) of the Public Health Service Act in April 2017. In response to a Complete Response Letter issued in February 2018, CELLTRION resubmitted the BLA in May 2018 with additional long-term efficacy and safety data from Study CT-P10 3.3 (in advanced FL) generated since the initial submission and new clinical data from Study CT-P10 3.4 (in LTBFL). Similarity is claimed to the reference product, Rituxan®, which was first licensed in the US in November 1997 (BLA #103705). The currently approved indications of Rituxan® (Rituxan® USPI, 2018) are:

- Non-Hodgkin's Lymphoma
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan® in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC)
- Rheumatoid Arthritis in combination with methotrexate in adult patients with moderately- to severely-active RA who have inadequate response to one or more TNF antagonist therapies
- Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and MPA in adult patients in combination with glucocorticoids
- Moderate to severe PV in adult patients[4]

The development program for CT-P10 is in line with the FDA guidance and the EU guidelines for biosimilar biological products and has been discussed with the FDA at multiple Biosimilar Product Development (BPD) meetings from 2014 to 2018. FDA guidance indicates that a biosimilar applicant may obtain licensure for fewer than all conditions of use for which the reference product is licensed (FDA, 2015; FDA, 2018). Due to the current intellectual property and exclusivity landscape, CELLTRION seeks licensure of CT-P10 for the Proposed Indications only. These are the indications presented in the draft label submitted in the May 29, 2018 351(k) BLA resubmission.

[4] This indication is protected by orphan drug exclusivity until June 07, 2025.

The Proposed Indications are:

- Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to CT-P10 in combination chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy

Accompanied by a rigorous scientific justification for extrapolation to non-studied indications, the totality of data supports the approval of CT-P10 as a biosimilar to Rituxan® for the Proposed Indications (Table 3).

Table 3: Summary of Fulfillment of Biosimilar Statutory Requirements by CT-P10 BLA

Statutory Requirement	Statute Language	CT-P10 BLA Fulfillment of Requirements
Reference Product	351(k)(5)(A) One reference product per application. A biological product, in an application submitted under this subsection, may not be evaluated against more than 1 reference product	The single reference product in the BLA for CT-P10 is Rituxan®. Some evaluations were performed using EU-approved MabThera®. A scientific "bridge" between Rituxan® and MabThera® has been established through extensive physicochemical and functional testing and through a PK similarity study comparing CT-P10, Rituxan® and MabThera® in patients with RA.
Analytical Data	351(k)(2)(A)(i)(I)(aa) Analytical studies demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components	The analytical data demonstrate that CT-P10 is highly similar to the reference product, Rituxan® from an analytical standpoint including primary and higher order structure, purity, stability and functional activities notwithstanding minor differences in clinically inactive components. These data also show that Rituxan® and MabThera® are structurally and functionally indistinguishable, providing the analytic component of the scientific bridge between Rituxan® and MabThera®, justifying the relevance of data from studies with MabThera®.
Animal Studies	351(k)(2)(A)(i)(I)(bb) Animal studies (including the assessment of toxicity)	CT-P10 was compared with MabThera® in a tissue binding study, and in a repeat-dose study conducted in cynomolgus monkeys which evaluated PD, toxicokinetics, toxicity and local tolerance. Non-clinical studies indicated that the pharmacologic and toxicologic profiles of CT-P10 and MabThera® are similar.

Statutory Requirement	Statute Language	CT-P10 BLA Fulfillment of Requirements
Clinical Studies	351(k)(2)(A)(i)(I)(cc) A clinical study or studies (including the assessment of immunogenicity and PK or PD) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product	Clinical studies were conducted to assess PK/PD similarity and immunogenicity, as well as clinical efficacy and safety of CT-P10. Controlled clinical trials were conducted in a total of 398 FL patients: 258 patients with LTBFL randomized to CT-P10 or Rituxan® (Study CT-P10 3.4), 140 patients with advanced FL randomized to CT-P10 or Rituxan® (Study CT-P10 3.3). In addition, 526 patients with active RA randomized to CT-P10, Rituxan® or MabThera® (Studies CT-P10 3.2, CT-P10 1.1 and extension study of CT-P10 1.1 [CT-P10 1.3]) provided additional PK and immunogenicity data. No clinically meaningful differences were observed in terms of PK/PD, efficacy, safety and immunogenicity.
Mechanism of Action	351(k)(2)(A)(i)(II) The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product	The therapeutic effect of rituximab in the Proposed Indications results from binding to CD20 and consequential effects on B-cells including B-cell depletion. Rituximab induced B-cell depletion is mediated by activities such as CDC, ADCC, ADCP and apoptosis. The functional activities of CT-P10 have been carefully and systematically assessed and are highly similar to those of Rituxan®.
Conditions of Use	351(k)(2)(A)(i)(III) The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product	CELLTRION seeks licensure of CT-P10 for the indications contained in the draft label submitted with its May 29, 2018 351(k) BLA resubmission only. These three indications ("Proposed Indications") are: o Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent o Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to CT-P10 in combination chemotherapy, as single-agent maintenance therapy o Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
Route of Administration, Dosage Form, and Strength	351(k)(2)(A)(i)(IV) The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product	CT-P10 has the same route of administration (intravenous), dosage form and strength as Rituxan®. The same premedication regimens, administration precautions and doses of background chemotherapies will apply to the Proposed Indications of CT-P10 as for the corresponding indications of Rituxan®.

Statutory Requirement	Statute Language	CT-P10 BLA Fulfillment of Requirements
Fulfillment of the Definition of "Biosimilar"	351(k) (2) The term 'biosimilar' or 'biosimilarity', in reference to a biological product that is the subject of an application under subsection (k), means—(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product	The CT-P10 BLA provides evidence of high similarity between CT-P10 and Rituxan® in physicochemical structure and function. The totality of the data establishes that there are no clinically meaningful differences between CT-P10 and Rituxan®.
Fulfillment of the Bridging Criteria	FDA biosimilar guidance on PK/PD clinical pharmacology data (2014): "If a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compares all three products (i.e., the proposed biosimilar product, the US licensed reference product, and the non-US licensed product) and is likely to also include PK and, if appropriate, PD study data for all three products"	Both FL studies (pivotal therapeutic equivalence Study CT-P10 3.4 in LTBFL patients and Study CT-P10 3.3 in advanced FL patients) were conducted against US-licensed Rituxan®. CELLTRION has generated comprehensive 3-way analytical data showing similarity between CT-P10, Rituxan® and MabThera® in structure and function and has established PK similarity based on 3 pairwise comparisons in a 3-way parallel group, double-blinded randomized controlled study in RA patients (Study CT-P10 3.2 [Part 1]; 189 patients). Therefore, an adequate scientific bridge between all 3 products has been established, supporting use of data from comparative studies of CT-P10 with MabThera®.

CT-P10 received a marketing authorization approval in the EU on February 17, 2017 (Truxima® SmPC, 2018).

2.2 Product Knowledge

2.2.1 Structural and Functional Characteristics of Rituximab

The active substance of CT-P10, Rituxan® and MabThera® is rituximab. Rituximab is a chimeric human-murine monoclonal antibody of subclass immunoglobulin (Ig) G1 that selectively binds with high affinity to CD20, which is found only on the surface of B-cells. Rituximab is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each

heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 213 amino acids with 5 cysteine residues. All cysteine residues in the heavy and light chains are involved in either intra- or inter-disulfide bonding and C-terminal lysine variation is observed.

The fragment antigen binding (Fab) domain of rituximab binds to the CD20 antigen on B lymphocytes and the fragment crystallizable (Fc) domain can bind to complement and Fc receptors. Binding of rituximab to both CD20 and complement proteins can result in CDC, and binding of rituximab to both CD20 and Fcγ receptors on immune effector cells can result in ADCC and antibody-dependent cellular phagocytosis (ADCP).

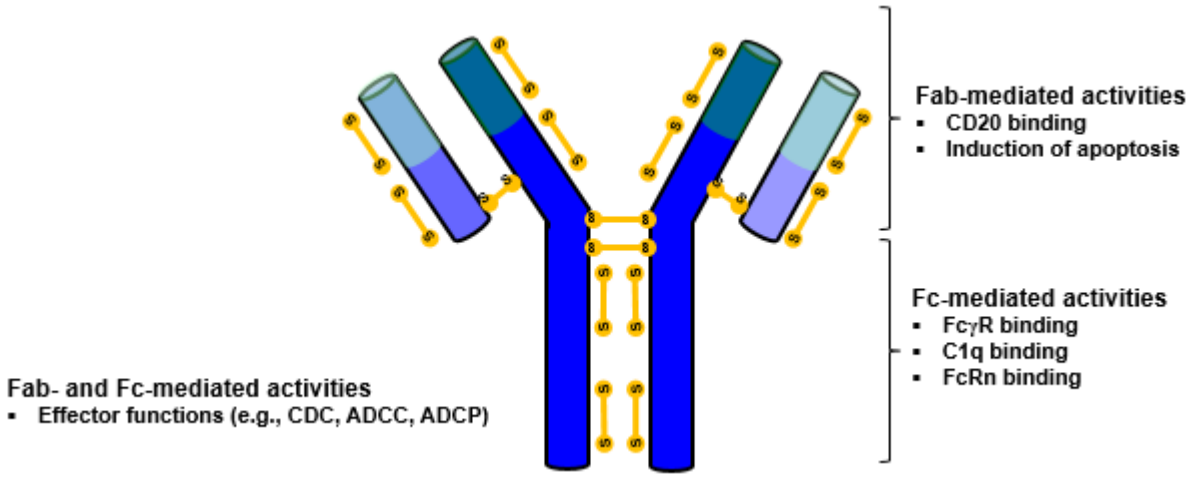


Figure 10: Schematic Diagram of the Structure of Rituximab with Functional Activities

2.2.2 Mechanisms of Action and B-cell Pathology across Conditions of Use

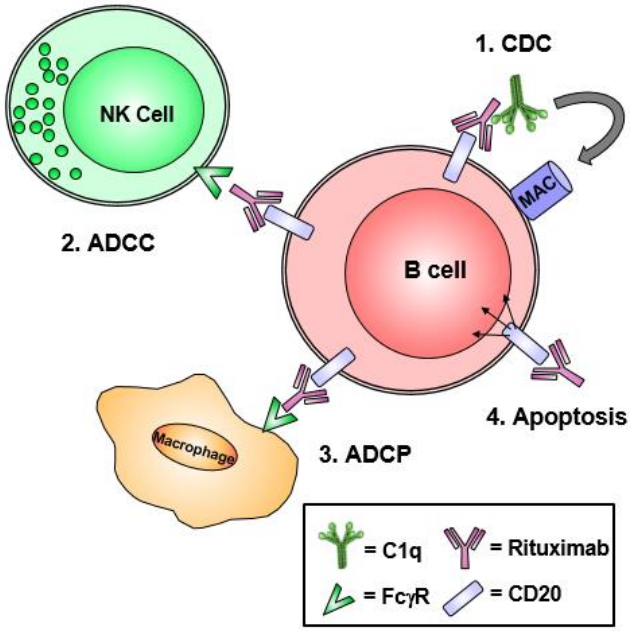
Rituximab binds to CD20, a hydrophobic transmembrane protein on the cell surface of B-cells.

CD20 is expressed on the surface of B-cells at all intermediate stages of differentiation starting from pre-B-cells through pro-plasma cells making these cells susceptible to rituximab (Burmester & Pezzutto, 2003); it is not found on the surface of B-cells in the initial or final stages of development (stem cells, pro-B cells, terminally differentiated plasma cells and plasmablasts). CD20 expressing B-cell lineages can give rise to malignancies (e.g., CLL and NHL) (Stashenko *et al*., 1980; Klein *et al.*, 2013).

CD20 is present on malignant B-lymphocytes in patients with certain mature B-cell lymphomas and leukemias. The therapeutic effect of rituximab across NHL conditions of use is mediated by binding to CD20, resulting in B cell death which ultimately leads to reduction of the tumor burden (Plosker & Figgit, 2003).

B-cell depletion in the Proposed Indications (Section 1.1) is driven by the same set of biological activities of rituximab. The binding of rituximab to CD20 and occupancy of CD20 on the surface of B-lymphocytes may result in elimination of these cells via CDC, ADCC, ADCP and/or apoptosis (Cartron *et al.*, 2004; Reff *et al.*, 1994; Taylor & Lindrofer, 2007). The activities responsible for B-cell depletion by rituximab have been extensively studied, and can be attributed to Fc and/or Fab functionality of rituximab as follows (Figure 11):

- Fab-Fc-mediated: CDC, ADCC and ADCP
- Fab-mediated: Induction of apoptosis of $CD20^{+}$ B-cells (now considered to be a minor activity)



Rituximab coated B-cells may be eliminated by different mechanisms. (1) CDC: Binding of rituximab to CD20 on B-cell surface causes activation of the complement cascade, which generates the membrane attack complex (MAC) that can directly induce B-cell lysis. (2) ADCC: Binding of rituximab allows interaction with effector cells such as natural killer (NK) cells via Fc gamma receptors (FcγR), which can lead to release of perforin and granzyme by the effector cell, resulting in lysis of the B-cell. (3) ADCP: Cells that are opsonized by the CD20 antibodies may be subject to ADCP, mediated by binding to Fc receptors on macrophages resulting in phagocytosis of the B-cell. (4) Apoptosis: The crosslinking of several molecules of rituximab and CD20 in the lipid raft may initiate the interaction of these complexes with signaling pathways that can weakly mediate direct apoptosis.

Figure 11: Mechanisms of Rituximab-mediated B-Cell Death (Adapted from Taylor & Lindrofer, 2007)

Therefore, a biosimilar product shown to be highly similar in terms of binding to CD20 and induction of CDC, ADCC, ADCP and apoptosis can be expected to have the same therapeutic effect as Rituxan® in the Proposed Indications for which CELLTRION seeks licensure (Section 1.1).

2.3 CT-P10 Manufacturing Information

CT-P10 was developed to be biosimilar to Rituxan®. CELLTRION established a Chinese hamster ovary (CHO) cell line for the production of CT-P10, similar to that used for the production of Rituxan®. The CT-P10 manufacturing process follows a standard procedure for monoclonal antibody production, starting from the thawing of a vial of the working cell bank followed by several cell expansion steps before final bioreactor production. The product is purified using multiple chromatography steps.

Critical quality attributes (CQAs) were first established based on risk assessment, data from early development, process characterization studies and information on commercial scale production. In-process controls (critical process parameters and critical in-process controls) and final release specifications were selected to ensure adequate control of these CQAs. Process validation studies were conducted to demonstrate the consistency of the manufacturing process in producing CT-P10 drug product that is highly similar to the reference product. The control strategy requires that all product complies with the predetermined specification and in-process acceptance criteria. Potential microbial contaminants are controlled and extraneous agents have been demonstrated to be sufficiently inactivated or removed by the manufacturing process.

During product development, changes to the manufacturing process were implemented and appropriate product characterization studies were conducted which demonstrated comparability of the product manufactured throughout development. Batches from the final commercial manufacturing process were included in analytical similarity studies and in clinical studies.

CT-P10 drug product is supplied in the same dosage form and strength as Rituxan®. It is provided as a sterile solution for injection as either 100 mg/10 mL in a single-use vial or 500 mg/50 mL in a single-use vial. The drug product formulation is identical to Rituxan® with respect to composition (pH 6.5, 25 mM sodium citrate, 154 mM NaCl, 0.07% polysorbate 80).

In summary, CT-P10 solution for injection is manufactured in accordance with GMP using a validated process with adequate controls to ensure the consistent commercial production of a product that is biosimilar to Rituxan® in the Proposed Indications (Section 1.1).

3 ANALYTICAL SIMILARITY

Overview

- Physicochemical and structural analyses using a comprehensive set of state-of-the-art, orthogonal methodologies confirmed that CT-P10 is highly similar to Rituxan®, as demonstrated by:
  - Identical primary structure;
  - Highly similar secondary and higher order structure;
  - Highly similar post-translational modifications with very small differences in deamidation at sites outside the Fab and Fc binding region;
  - Highly similar strength and content;
  - Highly similar purity and impurities with minor differences in levels of individual impurities which have no impact on efficacy, safety or immunogenicity;
  - Highly similar charge variants with slightly lower levels of acidic variants which have no impact on efficacy, safety or immunogenicity;
  - Highly similar glycosylation profile with a slightly higher N-linked mannose-5 glycan (Man5) content which was found to have no impact on the Fab- and Fc-related biological activities; and
  - A highly similar degradation and stability profile.
- Biological function analyses confirmed that CT-P10 is highly similar to Rituxan® in all relevant biological activities, namely:
  - CD20 binding (recombinant CHO-K1 cells expressing CD20);
  - Induction of apoptosis (using Raji [B lymphocyte] cells);
  - Fcγ receptor binding affinities (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa [V and F phenotype], FcγRIIIb, and FcRn);
  - C1q binding and CDC;
  - ADCC (using Raji cells as target cells and healthy donor peripheral blood mononuclear cells [PBMCs] as effectors; ADCC reporter assay); and
  - ADCP (using Raji cells as target cells and macrophages differentiated from peripheral blood monocytes as effector cells).
- Finally, CT-P10 and Rituxan® had similar CDC, ADCC and ADCP using primary human B-cells from PBMC of a healthy donor, a NHL patient, and a CLL patient as target cells, supporting similarity and extrapolation to the Proposed Indications of CT-P10 (Section 1.1).

The similarity studies were designed in line with principles outlined in FDA guidance documents on biosimilar products, FDA recommendations on statistical methods for analytical similarity assessments available in the public domain and principles of comparability assessment, as discussed in International Conference on Harmonisation (ICH) Q5E - *Comparability of biotechnological/biological products subject to changes in their manufacturing process* (2004). As CT-P10 was developed in a global program, 3-way comparisons between CT-P10, Rituxan® and MabThera® were included in the analytical similarity studies to establish a bridge between Rituxan® and MabThera®, and thus justify the relevance of data from comparative non-clinical studies of CT-P10 and MabThera®.

The physicochemical tests included in similarity studies comprised a range of orthogonal, state-of-the-art methodologies selected based on the known quality attributes of the reference product as shown in the Certificate of Analysis of MabThera® and methods included in the appendices of ICH Q6B – *Specifications: test procedures and acceptance criteria for biotechnological/biological products* (1999). The biological and functional assays included in analytical similarity studies were selected to measure all known and putative biological activities related to reported mechanisms of action.

A description of the test methods is provided in Appendix 1.

The analytical similarity program generally tested 15 lots each of CT-P10, Rituxan® and MabThera®. The number of lots included was determined by sample size calculations to obtain a statistical power of 90% and was based on the variability of the reference product in key assays. A greater number of lots were included in similarity studies than required by the sample size calculation. With the exceptions of protein concentration (n=12 for CT-P10), extractable volume (n=7 for Rituxan® and n=15 for CT-P10) and sub-visible particle analysis by micro-flow imaging (MFI) and light obscuration (n=12 for all products), all analytical tests were conducted using 15 lots of each product. CT-P10, Rituxan® and MabThera® lots used in clinical studies were included in the analytical similarity studies. As literature suggest that CD20 is expressed on B cells at different levels in different diseases (Prevodnik *et al*., 2011; Ginaldi *et al*., 1998; Karampetsou *et al*., 2011), additional studies were conducted using primary B-cells from the PBMC of a healthy donor, a NHL patient, and a CLL patient to support similarity and extrapolation to the Proposed Indications (Section 1.1). These additional studies were conducted using 3 lots of each product.

3.1 Tiering of the Analytical Similarity Attributes

Each product attribute measured by physicochemical, structural and functional tests, was ranked, in line with the ICH Q9 principles of risk assessment (2005), based on the potential for clinical impact. Criticality ranking considered the severity of the clinical impact and the likelihood that an out-of-range quality attribute would impact clinical performance. This assessment was based on data from literature and prior studies of CT-P10, Rituxan® and MabThera®.

All physicochemical structure attributes and biological functions were ranked as shown in Table 4, irrespective of whether statistical analysis of the test method data was possible.

Table 4: Quality Attributes and Their Criticality Classification

Criticality	Example of Quality Attributes (Clinical Relevance)
Very High	CD20 binding (efficacy), CDC (efficacy), ADCC (efficacy)
High	Primary structure (efficacy, safety, immunogenicity), protein concentration (efficacy), extractable volume (efficacy), ADCP (efficacy), C1q binding (efficacy), FcγRIIIa binding (efficacy)
Moderate	Secondary structure, thermal stability, tertiary structure, disulfide bond, free thiol content, deamidation, aggregates, fragments, particulates, host cell protein, host cell DNA, rProtein A, acidic variants, aglycosylation, afucosylation, agalactosylation, apoptotic activity, FcRn binding, FcγRIIIb binding, FcγRIIa binding, FcγRIIb binding
Low	Oxidation, monosaccharide, sialic acids, glycation, FcγRI binding
Very low	N-terminal glutamine variants, C-terminal lysine variants, basic variants

To establish similarity, data from each analytical method were assigned to tiers for statistical analysis, as follows:

Tier 1: Equivalence Test with the Null Hypothesis H_0: $\mu_T - \mu_R \leq -\delta$ or $\mu_T - \mu_R \geq \delta$.

- Where μ_T stands for mean of tested product; μ_R stands for mean of reference product; and δ stands for pre-determined equivalence margin (EM) based on variability of the reference product ($\pm$1.5*standard deviation [σ]).
- The confidence interval approach was used to determine whether the means for functional biological measures with CT-P10 and Rituxan® are similar.
- Similarity between 2 products was confirmed if the 90% CI of the mean difference was within the corresponding equivalence margin (- 1.5*σ, + 1.5*σ).

Tier 2: Quality Range Approach ($\mu_R - x\sigma_R$, $\mu_R + x\sigma_R$)

- Where μ_R stands for mean of reference product; σ_R stands for variation (standard deviation) of reference product; and x stands for multiplicity of unit reference product variation (multiplier).
- The quality range was set based on the reference product variation expressed as X times the standard deviation of 15 Rituxan® lots (mean of Rituxan® ± X*σ).
- "Two-sigma" and "three-sigma" approaches mean that 95.5% and 99.7% of values lie within 2 and 3 standard deviations of the mean, respectively (Tsong *et al*., 2015; Chow *et al*., 2015). Limits based on 4 sigma may be appropriate where reference product values have a narrow range and a wider range would have no clinical impact.
- The multiplier X applied to each test output was selected based on criticality of the attribute, method sensitivity and where relevant, the level of purity/impurity present.
- High similarity was considered to have been demonstrated where 90% or more of the data points were within the quality range.

Tier 3: Qualitative Comparison of Raw Data

- The raw data of quality attributes with a low criticality ranking and those derived from qualitative test methods were visually assessed.

Importantly, functional assays that measure activities related to the MoA or which could influence PK were subject to Tier 1 (equivalence test) or Tier 2 (quality range) statistical analysis.

The tier for statistical analysis of data from each test method is shown in Table 5.

3.2 Analytical Similarity Results

In addition to an assessment of the similarity of CT-P10 and Rituxan®, comparisons between CT-P10 and MabThera® and between MabThera® and Rituxan® were conducted, in accordance with FDA recommendations. A summary of results from statistical analysis of the data from each analytical test, according to the assigned tier, is presented in Table 5. This table shows whether data analyzed by Tier 1 equivalence test were within the EM, the % of lots within the quality range for data analyzed by the Tier 2 quality range approach, and the conclusions of visual examination for data analyzed by the Tier 3 approach.

The data from the extensive 3-way similarity studies demonstrated that CT-P10 is highly similar in quality to Rituxan® and MabThera®. Any differences observed during pairwise comparison of the quality attributes are discussed in detail below. None of these minor differences were assessed as being likely to have clinically-relevant impact.

Table 5: Results of Statistical Analyses of Analytical Similarity Assessment Data

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
Physicochemical & Structural Analysis							
Primary Structure	Peptide Mapping (HPLC)	Comparison of tryptic peptide map by visual inspection		3 – Qualitative comparison	High	High	High
	Amino Acid Analysis	Determination of amino acid composition		3 – Qualitative comparison	High	High	High
	Molar Absorptivity	Determination of molar absorptivity and extinction coefficient	Molar absorptivity	2 – % within Quality Range	93	93	100
			Extinction coefficient		93	93	100
	N-terminal Sequencing	Comparison of N-terminal sequences		3 – Qualitative comparison	High	High	High
	C-terminal Sequencing	Comparison of C-terminal sequences		3 – Qualitative comparison	High	High	High
	Intact Mass (LC-MS)	Molecular weight		3 – Qualitative comparison	High	High	High
Post-Translational Modification	Peptide Mapping (LC-MS)	Deamidation (%)	HC Asn55	2 – % within Quality Range	100	100	100
			HC Asn290		100	100	100
			HC Asn319		100	100	100
			HC Asn365		80 (<0.1% higher level)	80 (0.1% higher level)	100
			HC Asn388		87 (<0.3% lower level)	93	87 (<0.4% lower level)
			LC Asn136	3 – Qualitative comparison	High	High	High
		Oxidation		3 – Qualitative comparison	High	High	High
		N-terminal glutamine		3 – Qualitative comparison	High	High	High

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
		C-terminal lysine		3 – Qualitative comparison	High	High	High
Higher Order Structure	FTIR	Comparison of secondary structure		3 – Qualitative comparison	High	High	High
	DSC	Evaluation of thermal stability and determination of thermal transition temperatures	Transition 1 (°C)	2 – % within Quality Range	100	100	100
			Transition 2 (°C)		100	100	100
			Transition 3 (°C)		100	100	100
	CD	Comparison of secondary and tertiary structures		3 – Qualitative comparison	High	High	High
	Free Thiol Analysis	Comparison of the amount of free sulfhydryl groups		2 – % within Quality Range	100	100	100
	Disulfide Bonds	Comparison of disulfide bond location		3 – Qualitative comparison	High	High	High
Content	Protein Concentration (UV_{280})	Protein concentration (UV_{280})		2 – % within Quality Range	92	100	92
	Extractable Volume	Extractable volume (mL)		3 – Qualitative comparison	High	High	High

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
Purity / Impurity	SEC-HPLC	Determination of aggregate, fragment content and monomeric purity	Monomer (%)	2 – % within Quality Range	60 (<0.5% higher level)	100	87 (<0.3% higher level)
			HMW (%)		40 (<0.6% lower level)	100	47 (<0.4% lower level)
			LMW (%)		60 (<0.04% higher level)	100	33 (<0.06% higher level)
	SEC-MALS	Determination of aggregate/monomeric content and molecular weight	Monomer (%, UV)	2 – % within Quality Range	100	100	100
			HMW (%, UV)		100	100	100
			Monomer (%, MALS)		100	100	100
			HMW (%, MALS)		100	100	100
			Monomer (MW, kDa)		100	100	100
		Determination of molecular weight (HMW)		3 – Qualitative comparison	High	High	High
	AUC	Determination of aggregate/monomeric contents	Monomer (s-value)	2 – % within Quality Range	100	100	100
			Monomer (% Area)		100	100	93
			Dimer (s-value)		100	100	100
			Dimer (% Area)		100	100	93
	Non-reduced CE-SDS	Determination of electrophoretic mobility and purity under non-reducing conditions	% Peak 1+2+3+4+5	2 – % within Quality Range	87 (<2.4% lower level)	100	100
			% Intact IgG		87 (<2.4% higher level)	100	100
	Reduced CE-SDS	Determination of electrophoretic mobility and purity under reducing conditions	% Non-glycosylated HC	2 – % within Quality Range	7 (<0.4% higher level)	93	87 (<0.4% higher level)
			% H + L		7 (<0.4% lower level)	93	87 (<0.4% lower level)

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
	Residual Host Cell Protein	Determination of the level of residual host cell protein		3 – Qualitative comparison	High	High	High
	Residual Host Cell DNA	Determination of the level of residual host cell DNA		3 – Qualitative comparison	High	High	High
	Residual rProtein A	Determination of the level of residual rProtein A		3 – Qualitative comparison	High	High	High
	MFI	Comparison of the numbers of sub-visible particles		3 – Qualitative comparison	High	High	High
	Light Obscuration			3 – Qualitative comparison	High	High	High
Charge Variants	IEF	Comparison of isoelectric point(s)		3 – Qualitative comparison	High	High	High
	IEC-HPLC	Comparison of charge variant distribution (Peak 1+2+3)		2 – % within Quality Range	7 (<4.5% lower level)	100	20 (<4.3% lower level)
		Comparison of charge variant distribution (Peak 4, 5, 6, 7)		3 – Qualitative comparison	High	High	High
Glycosylation	Oligosaccharide Profiling	Comparison of glycosylation patterns	% G0F	2 – % within Quality Range	100	100	100
			% G0		100	100	100
			% Man 5		0 (<1.5% higher level)	100	0 (<1.6% higher level)
			% G0+Man5		53 (<1.1% higher level)	100	33 (<1.2% higher level)
			% G1F		100	100	100
			% G2F		100	100	100
	N-linked Glycan Analysis	Comparison of oligosaccharide structures, attachment sites and distribution	% G0F	2 – % within Quality Range	100	100	100
			% G1F		100	100	100
			% G2F		100	100	100

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
			% Man5		0 (<1.9% higher level)	100	0 (<1.9% higher level)
			% G0		100	100	100
			% G0+Man5		0 (<1.5% higher level)	100	7 (<1.5% higher level)
		Comparison of oligosaccharide structures, attachment sites and distribution	% G1F+NANA	3 – Qualitative comparison	High	High	High
			% G2F+NANA		High	High	High
			% G2F+2NANA		High	High	High
	Sialic Acid Analysis	Determination of sialic acid content		3 – Qualitative comparison	High	High	High
	Monosaccharide Analysis	Comparison of neutral and amino sugar composition		3 – Qualitative comparison	High	High	High
	Glycation Analysis	Comparison of glycation level		3 – Qualitative comparison	High	High	High
Biological & Functional Analysis							
Fab Binding	Cell-based CD20 Binding (CELISA)	% Relative binding by (%, EC_{50})		2 – % within Quality Range[2]	100	100	100
	Apoptosis using Raji cell (FACS)	% Relative apoptotic cells (%, apoptotic cells)	0.01 µg/mL	2 – % within Quality Range	100	100	100
			0.04 µg/mL		100	100	100
			0.13 µg/mL		100	100	100
Fc Binding	C1q Binding (ELISA)	% Relative binding (%, EC_{50})		2 – % within Quality Range	100	100	100
	FcγRIIIa-V Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100

Attribute	Assay	Measurement		Tier[1]	Analytic Similarity CT-P10 vs. Rituxan®	Analytic Bridge MabThera® vs. Rituxan®	Analytic Bridge CT-P10 vs. MabThera®
	FcγRIIIa-F Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100
	FcγRIIIb Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100
	FcγRIIa Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100
	FcγRIIb Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100
	FcγRI Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		3 – Qualitative comparison	High	High	High
	FcRn Binding Affinity (SPR)	% Relative binding affinity (%, K_D)		2 – % within Quality Range	100	100	100
Fab-Fc Mediated Activities	CDC using WIL2-S Cell	% Relative CDC (%, EC_{50})		1 – Equivalence Test	Within EM	Within EM	Within EM
	ADCC using PBMC	% Relative ADCC (%, cytotoxicity)	0.010 μg/mL	1 – Equivalence Test	Within EM	Within EM	Within EM
			0.035 μg/mL		Within EM	Within EM	Within EM
			0.122 μg/mL		Within EM	Within EM	Within EM
	ADCC Reporter Assay	% Relative reporter activity (%, EC_{50})		2 – % within Quality Range[2]	100	100	100
	ADCP using Raji Cell	% Relative ADCP (%, phagocytosis)	1.56 ng/mL	2 – % within Quality Range	100	100	100
			6.25 ng/m		100	100	100
			25.0 ng/mL		100	100	100

[1] For Tier 1 analysis, the 90% CI of the mean difference between the 2 products was required to be within the EM ($\pm 1.5\sigma_R$ of the reference product). For Tier 2 analysis, the percentage of data points within the quality range was calculated for the test product. Quality range limits were set at X * SD, where X=3 unless otherwise indicated.
[2] X=2.

3.2.1 Physicochemical and Structural Attributes

3.2.1.1 Primary Structure

CELLTRION used a range of techniques to compare the primary structure of CT-P10, Rituxan® and MabThera®, which include: peptide mapping (high-performance liquid chromatography [HPLC] and liquid chromatography-mass spectrometry [LC-MS]), determination of intact mass, amino acid analysis, molar absorptivity, N-terminal sequencing and C-terminal sequencing. The results demonstrated that CT-P10 drug product is identical to Rituxan® and MabThera® in primary structure, as shown in Figure 12, Figure 61 and Figure 62. The deoxyribonucleic acid (DNA) sequence of the CT-P10 cell banks was also confirmed to be the same as that of rituximab, based on the published amino acid sequence.

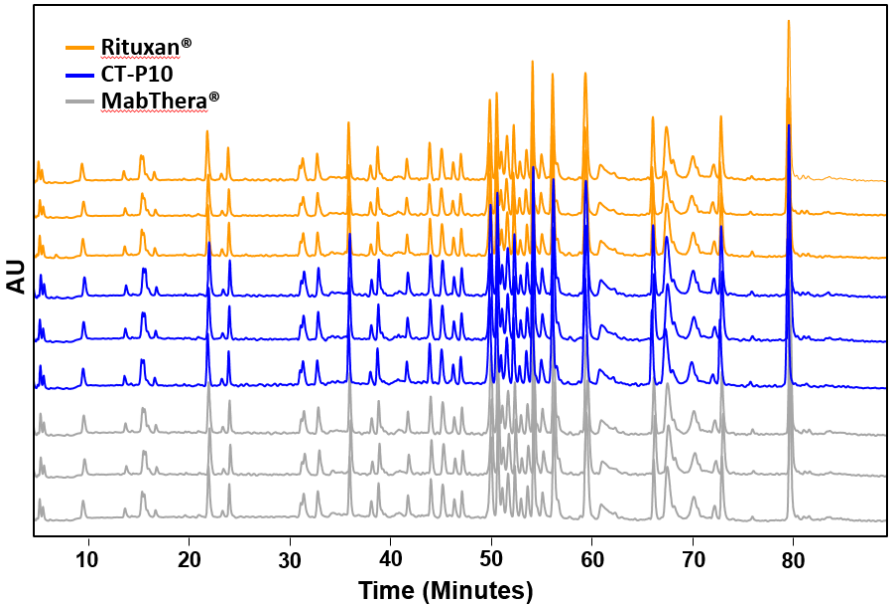


Figure 12: Chromatogram of Peptide Mapping by HPLC of Representative Lots of CT-P10, Rituxan® and MabThera®

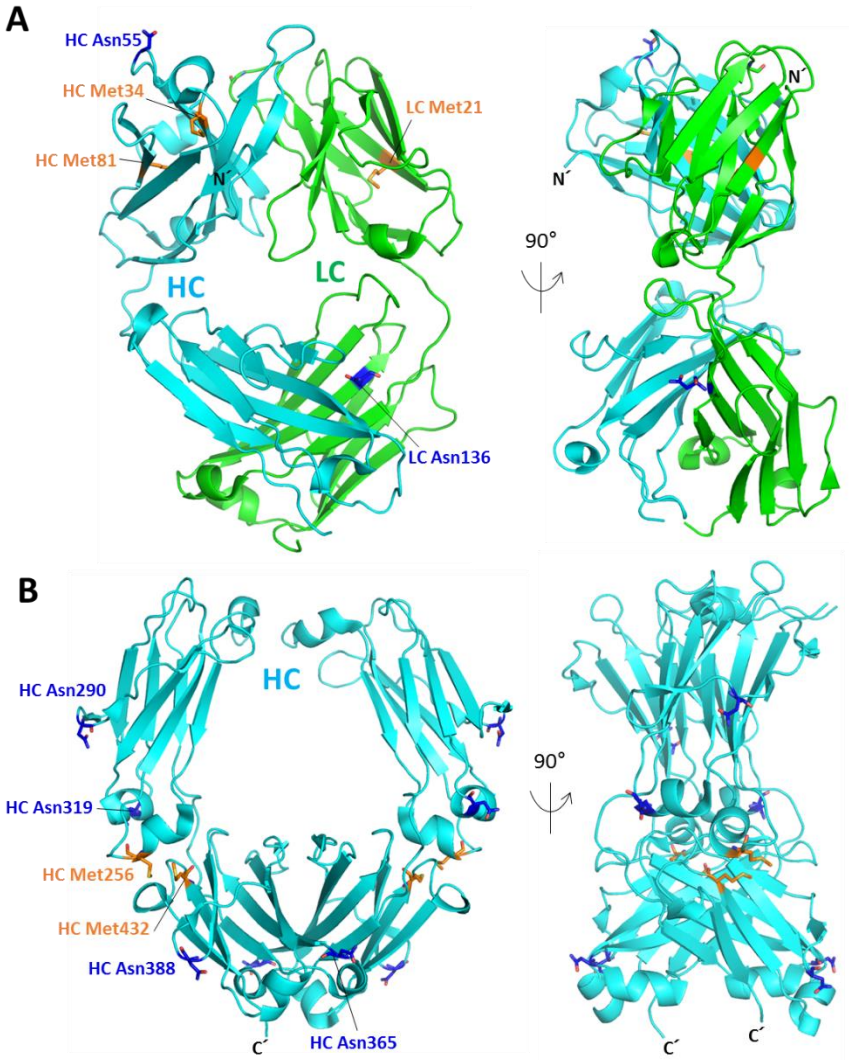
3.2.1.2 Post-translational Modifications

Peptide mapping by LC-MS was used to identify the post-translational modifications (PTM) of CT-P10, Rituxan® and MabThera®. The results show highly similar post-translational modifications in the 3 products. Some CT-P10 lots had higher levels of deamidated Asn365 (<0.1% difference in mean values) and lower levels of deamidated Asn388 (<0.3%). However, the levels of deamidation of heavy-chain (HC) Asn365 of CT-P10 and MabThera® were also observed in some Rituxan® lots. Furthermore, as Asn365 and Asn388 are located outside the Fab and Fc binding regions, deamidation at these sites is unlikely to be clinically relevant.

The data also indicate that CT-P10 contains slightly higher (<1.8%) levels of N-terminal glutamine in the light chain (LC Gln01) compared to Rituxan® and MabThera®, but all CT-P10 lots were within the quality range of Rituxan®. According to the literature, N-terminal pyro-glutamate has no effect on antibody structure or antigen binding (Lyubarskaya *et al.*, 2006), and no differences in *in vivo* clearance between antibodies with N-terminal glutamine and antibodies with N-terminal pyro-glutamate have been reported (Liu *et al.*, 2011).

Finally, the levels of oxidized amino acids in CT-P10 are highly similar to those of Rituxan® and MabThera®.

Overall, any minor differences in levels of deamidation and N-terminal pyro-glutamate between the three products had no impact on biological and functional activities, which were shown to be highly similar, as described in Section 3.2.2.



(A) Residues where PTM are detected are shown in stick on the Fab structure (from PDB_2OSL).
(B) Residues of where PTM are detected are shown in stick on Fc structure (from PDB_3SGJ). Deamidation sites (HC Asn55, HC Asn290, HC Asn319, HC Asn365, HC Asn388, and LC Asn136) are labeled in blue, oxidation sites (HC Met34, HC Met81, HC Met256, HC Met432, and LC Met21) are labeled in orange and the N- and C-terminus of the structure are marked by N´ and C´, respectively.

Figure 13: Schematic Diagrams Showing Sites of Post-Translational Modification in CT-P10, Rituxan® and MabThera®

3.2.1.3 Higher Order Structure

The higher order structures of CT-P10, Rituxan® and MabThera® were compared using free thiol analysis and the positions of disulfide bonds were assessed using native and reduced peptide mapping. In addition, the secondary and tertiary structures of the molecule were analyzed by Fourier Transform Infra-Red (FTIR), near and far ultraviolet (UV) circular dichroism (CD) and differential scanning calorimetry (DSC). No differences in the higher order structure were observed as shown in Figure 14 and Figure 63 through Figure 65.

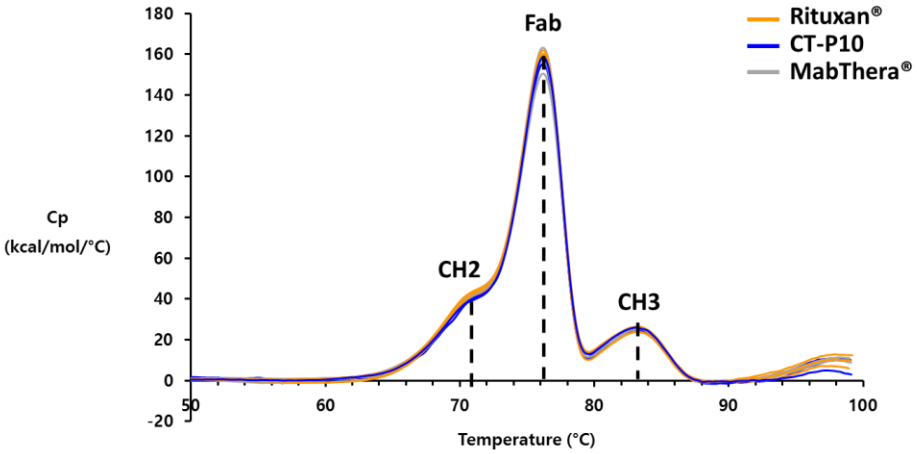
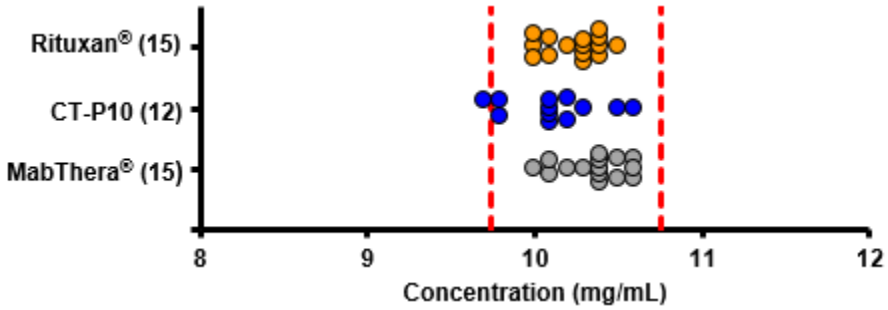


Figure 14: DSC Thermograms of Representative Lots of CT-P10, Rituxan® and MabThera®

3.2.1.4 Protein Content

The CT-P10 drug product manufacturing process was adjusted to match the protein concentration of CT-P10 with that of Rituxan® to ensure the final strength of rituximab in CT-P10 is the same as the reference product. Similarity of protein concentration was therefore evaluated using 12 lots of CT-P10 and 15 lots each of Rituxan® and MabThera®. Figure 15 shows a scatter plot of the data with a row for the data from each product and the quality range of Rituxan® lots marked with dashed vertical lines. As shown in Figure 15, over 90% of CT-P10 lots were within the Tier 2 quality range, with a single outlier that was within 0.04 mg/mL of the quality range of Rituxan®. The protein concentration of CT-P10 was highly similar to that of Rituxan® after the manufacturing process adjustment.

The extractable volumes of CT-P10 and Rituxan® were highly similar, ensuring that the same amount of rituximab will be delivered on administration of the 2 products.



Notes: Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots. Number of lots used in the similarity study is indicated in brackets.

Figure 15: Protein Concentration of CT-P10, Rituxan® and MabThera®

3.2.1.5 Purity/Impurity Profile

Product monomer, high molecular weight (HMW) and low molecular weight (LMW) content were determined using size exclusion chromatography (SEC)-HPLC, SEC-MALS and analytical ultracentrifugation (AUC).

Results indicated that there were no significant differences in the level of monomer, HMW and LMW forms among CT-P10, Rituxan® and MabThera®. The slightly lower (<0.6%) HMW content and higher monomer content in CT-P10 detected by SEC-HPLC (Figure 66) was not corroborated by the other methods, and had no impact on biological and functional activities (Section 3.2.2), or on immunogenicity and safety in clinical studies (Section 5.4).

The amount of intact IgG, non-glycosylated heavy chain (NGHC) and sum of heavy and light chains (H+L) were evaluated by non-reduced/reduced capillary electrophoresis sodium-dodecyl sulfate (CE-SDS). The data suggested that CT-P10 has a slightly higher level of intact IgG and lower level of fragments than Rituxan® and MabThera®, although this is unlikely to be clinically meaningful. Lower levels of H+L and slightly higher levels of NGHC were detected in CT-P10, but the magnitude of these differences was very small (<0.4%) and had no impact on biological and functional activities (Section 3.2.2).

Process related impurities including host cell protein, host cell DNA and rProtein A were also evaluated. The levels of these impurities in CT-P10 were very low and were highly similar to those of Rituxan® and MabThera®.

Finally, similar levels of sub-visible particles were detected in CT-P10, Rituxan® and MabThera® using MFI (Figure 67) and light obscuration (Figure 69).

3.2.1.6 Charge Variants

High-resolution isoelectric focusing (IEF) and highly sensitive ion-exchange chromatography (IEC-HPLC) methods were used to assess variants based on their surface charge.

IEF analysis showed that the calculated isoelectric point (pI) values of the 3 bands were similar and fell within similar ranges for CT-P10, Rituxan® and MabThera®. Slight differences in the level of the 7 charge variant peaks were detected by IEC-HPLC (Figure 16), with CT-P10 containing lower (<4.5%) levels of acidic peaks (Peak 1, Peak 2, Peak 3) and higher levels of basic peaks (Peak 5, Peak 6, Peak 7). However, peak characterization studies showed that all charge variants are biologically active and thus small differences in charge variants are unlikely to be clinically meaningful. In addition, deamidation of recombinant monoclonal antibodies is known to occur *in vivo* and is observed for endogenous IgG (Liu *et al*., 2014), supporting the safety of such variants.

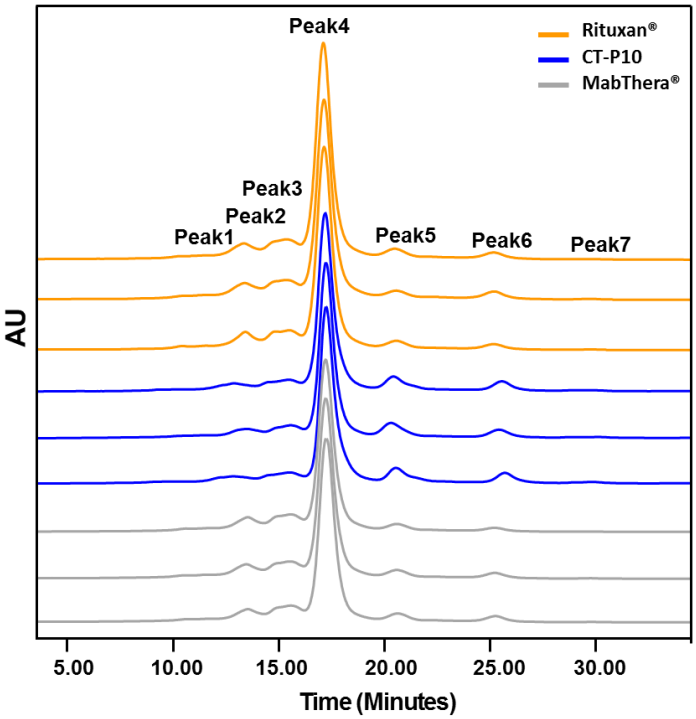


Figure 16: Seven Charge Variant Peaks of Representative Lots of CT-P10, Rituxan® and MabThera®

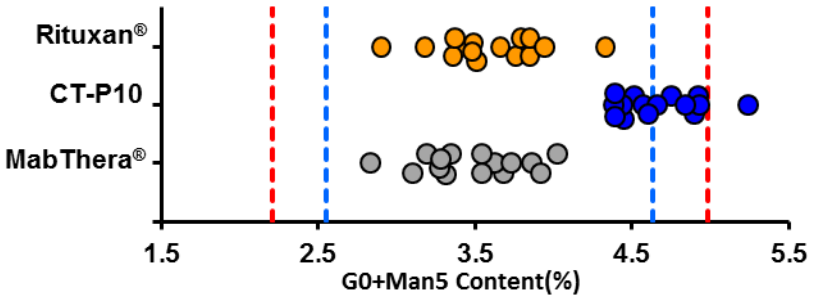
3.2.1.7 Glycosylation

CT-P10, like other IgG1 subclass antibodies, is a glycoprotein. The glycan micro-heterogeneity associated with N-glycosylation was characterized by High-Performance Anion Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD) and N-linked glycan analysis.

CT-P10, Rituxan® and MabThera® contain mostly G0F and G1F structures; minor species including Man5, G2F, G0 and G1 were also detected as shown in Figure 70.

All CT-P10 lots were within the quality range of Rituxan® and MabThera® with respect to glycan content, with the exception of Man5. CT-P10 had approximately 1.5% higher levels of Man5 by HPAEC-PAD and although within the mean ± 3SD quality range of Rituxan®, the mean content of G0 in CT-P10 was approximately 0.5% lower than that of Rituxan®. Nevertheless, the higher Man5

impacted statistical similarity of G0+Man5, with approximately 50% of the CT-P10 lots outside the quality range of Rituxan® and the overall afucosylated glycan content of CT-P10 was <1.1% higher than in Rituxan®. However, an afucosylation study (Section 3.2.1.8) indicated that at the levels present in the products, G0+Man5 had no impact on biological and functional activities. As shown in Figure 17, data from all but 1 lot of CT-P10 were within the mean± 4SD range of Rituxan® lots. Importantly, high similarity was detected across CT-P10, Rituxan® and MabThera® in FcγRIIIa binding affinity, ADCC and ADCP (Section 3.2.2), demonstrating that the minor difference in Man5 content is not clinically meaningful, as was confirmed by clinical studies (Section 5).



Notes: Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted blue lines and red lines represent the quality range limits based on mean ± 3SD and mean ± 4SD of Rituxan® lots, respectively.

Figure 17: Afucosylated Glycan (G0+Man5) Content of CT-P10, Rituxan® and MabThera®

Results of sialic acid analysis demonstrated that the most commonly occurring form of neuraminic acid in CT-P10, Rituxan® and MabThera® is N-acetylneuraminic acid (NANA). Levels of NANA were very low and highly similar in all 3 products.

Monosaccharide analysis identified highly similar molar ratios of fucose (Fuc), N-acetylglucosamine (GlcNAc), galactose (Gal) and mannose (Man) in all 3 products.

Reduced intact mass analysis showed similar and low levels of glycation of lysine residues in Rituxan® and MabThera®. The levels of glycation in CT-P10 were slightly lower (approximately 0.5% for the heavy chain and 1% for the light chain) than those of Rituxan® and MabThera®. Analysis of the glycation sites of CT-P10 showed that the glycation sites are not within either the CD20 or Fc receptor binding regions and as expected, the small difference in level of glycation had no impact on biological or functional activities (Section 3.2.2).

3.2.1.8 Glycosylation-Associated Biological Activities

The impact of amannosylation, asialylation, agalactosylation, and aglycosylation on Fc and Fab functionality of CT-P10, Rituxan® and MabThera® was assessed using mannosidase, β-1,4-galactosidase, neuraminidase and peptide: N-Glycosidase F (PNGase F) treatment of 1 lot of each product.

There was no significant correlation between levels of terminal mannose or sialic acid and CD20, FcRn, FcγRIIIa or C1q binding. Complete removal of terminal galactose slightly reduced FcγRIIIa binding affinity in all 3 products but had no impact on other activities. The 3 products responded in a similar manner to galactosidase, mannosidase and neuraminidase treatment, supporting similarity of the glycan profile of CT-P10, Rituxan® and MabThera®.

Deglycosylation of CT-P10, Rituxan® and MabThera® by PNGase F resulted in similarly reduced FcγRIIIa and C1q binding, and slightly reduced FcRn binding affinity, again supporting similarity of the glycan profiles of the products. Notably, a 5% difference in NGHC levels of the deglycosylated samples had no significant impact on biological and functional activities indicating that the small difference in NGHC content of CT-P10 and Rituxan® (< 0.4%) is not clinically meaningful, as was confirmed by similarity studies of biological and functional activities (Section 3.2.2), and by clinical studies (Section 5).

In a study of the impact of afucosylated glycans on FcγRIIIa binding affinity and ADCC using samples with artificially induced high levels of afucosylated glycans, a linear relationship between afucosylated glycans and FcγRIIIa binding affinity and ADCC was established. However, at the levels of afucosylated glycans observed in CT-P10, Rituxan® and MabThera®, no statistical correlation was found, indicating that the very small difference among the 3 products in afucosylated glycan content is not biologically relevant. Therefore, the slightly higher (<1.1%) content of afucosylated glycans (G0+Man5) detected in CT-P10 is unlikely to have clinical impact, as was confirmed by similarity studies of biological and functional activities (Section 3.2.2), and by clinical studies (Section 5).

3.2.1.9 Thermal Stability and Degradation Profile

The stability profiles of CT-P10, Rituxan® and MabThera® were compared in stability studies under accelerated and stress conditions, and in forced degradation studies, as summarized in Table 6. Additionally, the purity/impurity profiles and CDC of CT-P10 and MabThera® were compared in stability studies at real-time/real-temperature conditions.

Table 6: Summary of Comparative Stability Studies of CT-P10, Rituxan® and MabThera®

Stability Studies	Conditions	Duration	CT-P10	Rituxan®	MabThera®	Stability Profile
Real-Time / Real-Temperature	5 ± 3 °C	36 months	✓	Not tested	✓	Comparable
Accelerated	25 ± 2°C / 60 ± 5% RH	6 months	✓	✓	✓	Comparable
Stressed	40 ± 2°C / 75 ± 5% RH	3 months	✓	✓	✓	Comparable

Stability Studies	Conditions	Duration	CT-P10	Rituxan®	MabThera®	Stability Profile
Forced Degradation	Hydrogen Peroxide	6 hours	✓	✓	✓	Comparable
	UV Light	10 hours	✓	✓	✓	Comparable
		20 hours	✓	✓	✓	Comparable
	50°C	24 hours	✓	✓	✓	Comparable
		60 hours	✓	✓	✓	Comparable
	pH 3.3, 25°C	10 hours	✓	✓	✓	Comparable
		20 hours	✓	✓	✓	Comparable
	pH 10.5, 25°C	48 hours	✓	✓	✓	Comparable
		96 hours	✓	✓	✓	Comparable

Notes: Agitation and freeze-thaw stress conditions were tested during formulation development and had no impact on product quality attributes as was confirmed by shipping validation studies and additional freeze-thaw studies.

There were no differences in the stability profiles of CT-P10 and MabThera® stored under real-time/real-temperature conditions.

Under accelerated conditions, at temperatures higher than those used for storage of CT-P10, Rituxan® and MabThera®, there were slight trends observed in purity by non-reduced and reduced CE-SDS, in charge variants by IEC-HPLC and in CDC. The changes were comparable across all 3 products.

Under stress conditions, at temperatures significantly higher than those used for storage of CT-P10, Rituxan® and MabThera®, there were discernible changes in purity by SEC-HPLC, non-reduced CE-SDS, and in charge variants by IEC-HPLC as shown in Figure 18 through Figure 20. The data demonstrate comparable changes in the quality attributes of the 3 products over time.

Overall, there were no discernable differences in the degradation profiles of CT-P10, Rituxan® and MabThera® under any storage condition.

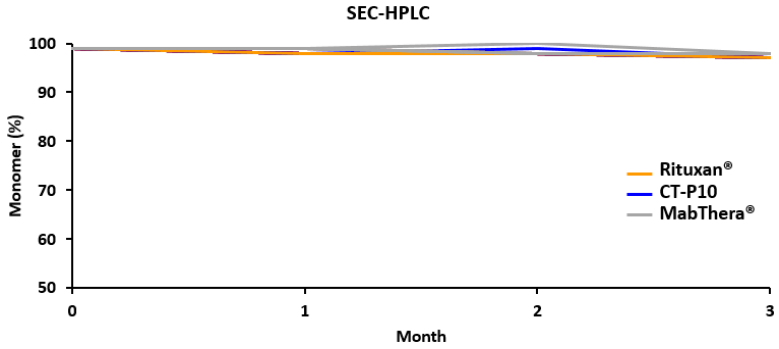


Figure 18: SEC-HPLC Trend Analysis of CT-P10, Rituxan® and MabThera® under Stress (40 ± 2°C / 75 ± 5% RH) Conditions

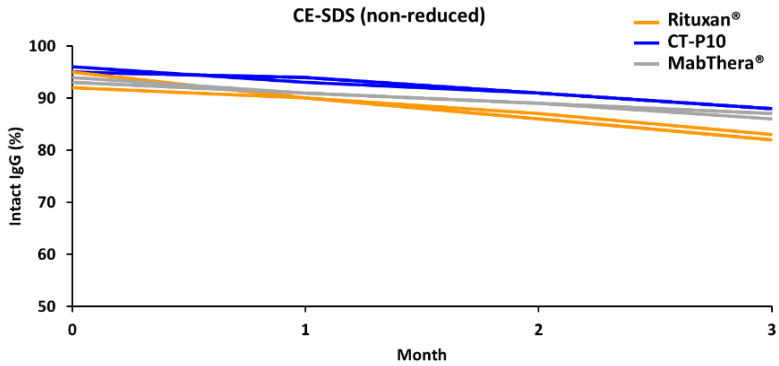


Figure 19: Non-reduced CE-SDS Trend Analysis of CT-P10, Rituxan® and MabThera® under Stress (40 ± 2°C / 75 ± 5% RH) Conditions

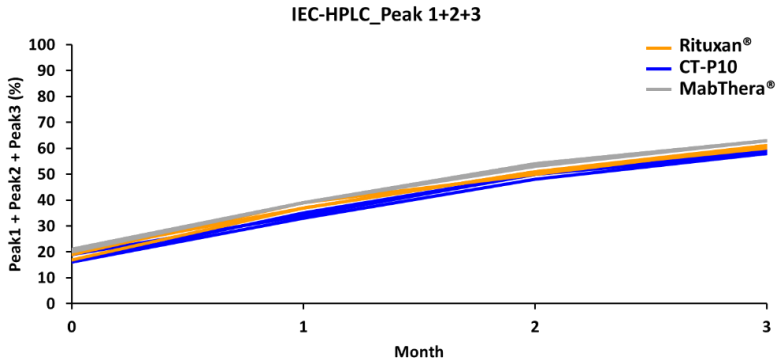


Figure 20: IEC-HPLC Trend Analysis of CT-P10, Rituxan® and MabThera® under Stress (40 ± 2°C / 75 ± 5% RH) Conditions

A forced degradation study was performed to characterize the degradation pathways of CT-P10, Rituxan® and MabThera®. This study was conducted using 1 lot of each product under oxidative (0.005 and 0.01% H_2O_2), light (20 w/m²), high temperature (50°C), low pH (pH 3.3) and high pH (pH 10.5) degradation conditions. Changes observed under each stress condition were comparable across the 3 products, demonstrating similarity in degradation profiles and further supporting the

structural similarity of these products. The conclusions of this study were confirmed by an additional forced degradation study using 2 lots of each product.

3.2.2 Biological & Functional Activities

The modes of action of rituximab leading to B-cell depletion, as identified through a systematic literature search, can be attributed to Fab and Fc functions and include induction of CDC and ADCC. ADCP and apoptosis of CD20+ B-cells may also contribute to rituximab-mediated B-cell depletion. The fact that CT-P10 and Rituxan® are highly similar in all these activities against both normal and malignant B-cells, strongly supports the premise that CT-P10 and Rituxan® can be expected to have a highly similar therapeutic effect in the Proposed Indications (Section 1.1).

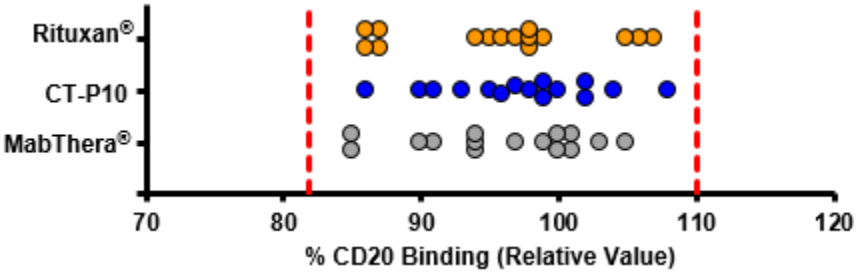
Studies were conducted to assess CD20 binding, as well as activities resulting from CD20 binding, including CDC, ADCC, ADCP and apoptosis induction by CD20 signaling, a putative MoA. In addition, binding to C1q and Fc receptors were evaluated. To reduce intra-assay variability, an internal reference standard was included in functional assays and the results for CT-P10, Rituxan® and MabThera® were calculated relative to the internal reference standard. Several assays were conducted using multiple concentrations of the products in the linear dose range to ensure robust assessment of similarity. Descriptions of the test methods are provided in Appendix 1.

3.2.2.1 Fab-mediated Binding

CD20 binding

CD20 binding initiates several signaling cascades and exposes the Fc portion of the antibody to interaction with Fcγ receptors of the immune effector system, opening up the potential for C1q initiated CDC, as well as ADCC and ADCP.

Binding to CD20 was evaluated in a CELISA using a CHO-K1 cell line expressing recombinant CD20 antigen. Tier 2 statistical analysis demonstrated that there were no differences in CD20 binding (Figure 21). All lots of CT-P10 and MabThera® were within the stringent quality range (mean ± 2SD) of Rituxan®; all CT-P10 drug product lots were also within the quality range (mean ± 2SD) of MabThera®. Therefore, the 3 products are highly similar in binding to CD20. As CD20 binding is essential for rituximab to exert its therapeutic effect, these data suggest that the efficacy of CT-P10 and Rituxan® will be similar in the Proposed Indications (Section 1.1).



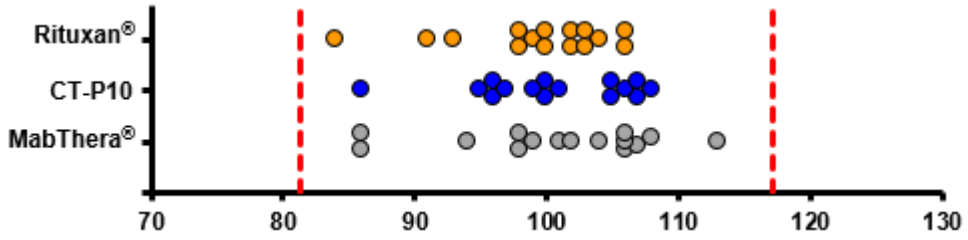
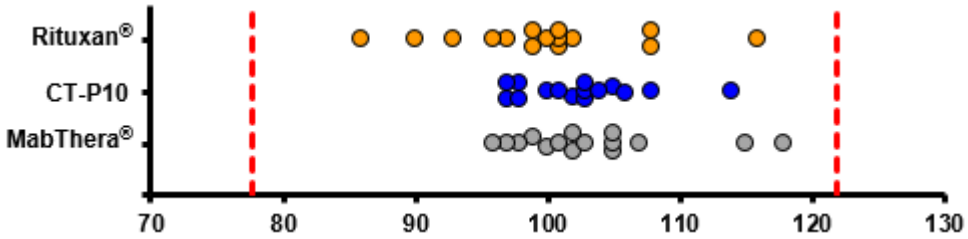
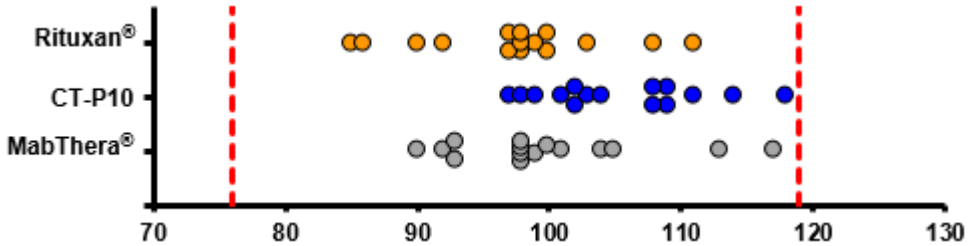
Notes: Relative binding to CD20 was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 2SD of the Rituxan® lots.

Figure 21: Relative Cell-based CD20 Binding (CELISA)

Apoptosis

The apoptosis induced by CD20 binding was evaluated using the Raji cell line (B lymphoblast-like cells from Burkitt's lymphoma patient). Flow cytometric analysis was performed and the percentage of apoptotic cells (Annexin V-FITC+/PI-) was used to quantify apoptosis of 3 concentrations of CT-P10, Rituxan® and MabThera®.

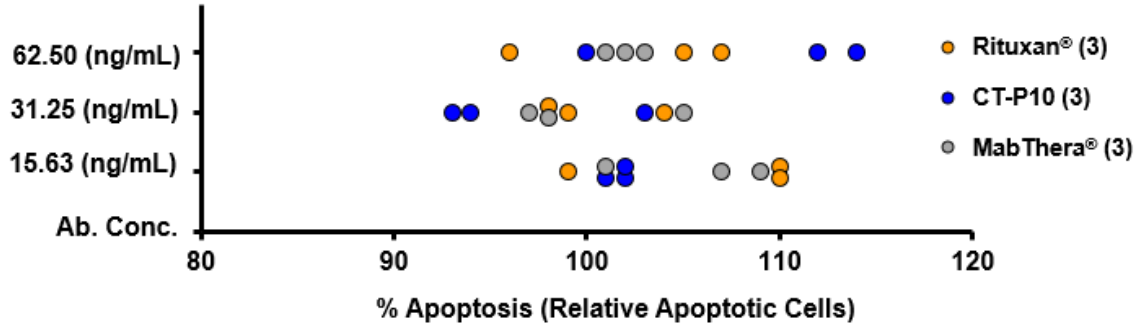
Statistical analysis of the data showed that CT-P10 and MabThera® were within the quality range (mean ± 3SD) of Rituxan®, indicating that all 3 products have highly similar apoptotic activities (Figure 22).

Ab. Conc.	% Apoptosis (Relative Apoptotic Cells)
0.13 µg/mL	
0.04 µg/mL	
0.01 µg/mL	

Notes: Relative percentage of apoptotic cells was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 22: Relative Apoptosis using Raji Cell Line

As shown in Figure 23, CT-P10, Rituxan® and MabThera® also induced comparable levels of apoptosis in MEC-2 B-cells at 3 antibody concentrations, further supporting similarity.



Notes: Relative percentage of apoptotic cells was determined against *in-house* reference standard. Statistical analysis was not performed due to the limited number of lots. Number of lots used in the additional study is indicated in brackets. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 23: Relative Apoptosis using MEC-2 B-cells at Multiple Antibody Concentrations

3.2.2.2 Fc-mediated Binding

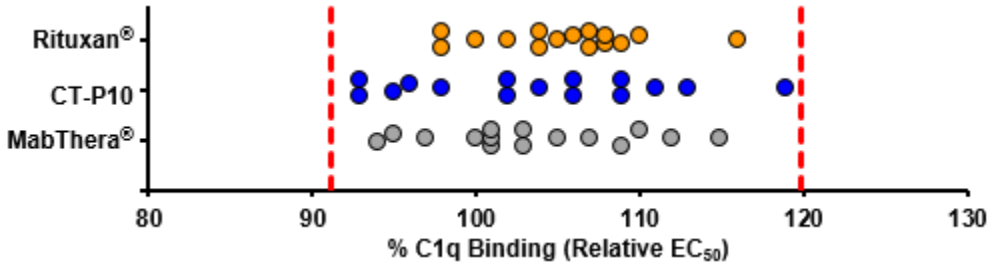
A large body of evidence, including pre-clinical and clinical studies, indicates that B-cell depletion as a consequence of binding to CD20 and interaction of the Fc region with complement (C1q) or Fc receptors, is a significant MoA of rituximab.

C1q is predominantly synthesized by peripheral tissue macrophages and dendritic cells (Lu *et al.*, 2007) with a widespread tissue distribution. Binding of rituximab to CD20 on a B-cell and interaction of the Fc region with C1q initiates the classical complement pathway resulting in lysis of the B-cell.

Fc receptors are present on a number of cells in the immune system including phagocytes such as macrophages and monocytes, granulocytes such as neutrophils and eosinophils, and lymphocytes of the innate immune system (e.g., natural killer cells) or adaptive immune system (e.g., B-cells; Selvaraj *et al.*, 2004; Sarfati *et al.*, 1992). Binding to Fcγ receptors mediates a range of effects including ADCC through degranulation of effector cells and subsequent elimination of antibody coated target cells. ADCP is mediated upon macrophage activation.

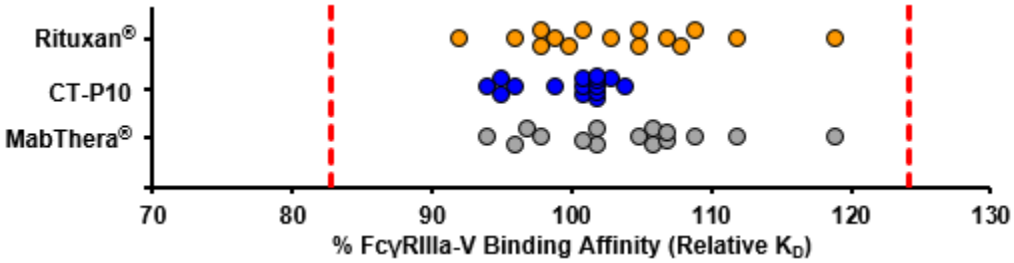
Binding of antibodies to FcRn is important in protecting IgG from lysosomal degradation and can influence PK (Roopenian & Akilesh, 2007). Thus, binding of CT-P10, Rituxan® and MabThera® to FcRn was evaluated to support the similarity of the products with respect to PK.

Statistical analysis using the Tier 2 (quality range) approach showed high similarity between CT-P10, Rituxan® and MabThera® in C1q binding, FcγRIIIa (V and F type) binding affinity and FcRn binding affinity. As illustrated in Figure 24 through Figure 27, all CT-P10 and MabThera® lots fell within the quality range (mean ± 3SD) of Rituxan® in these activities.



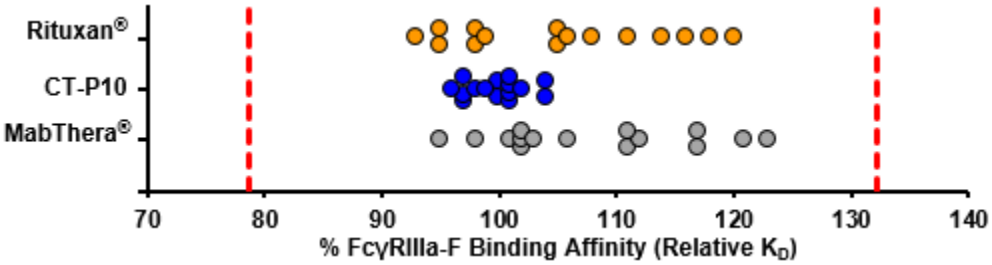
Notes: Relative C1q binding was determined against CT-P10 *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 24: Relative C1q Binding



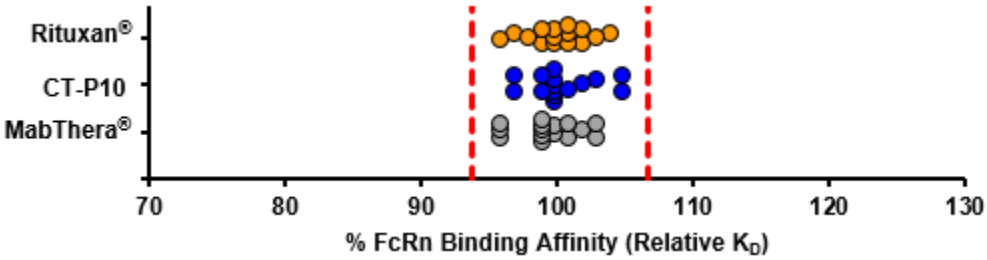
Notes: Relative K_D was determined against CT-P10 *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 25: Relative FcγRIIIa-V Binding Affinity



Notes: Relative K_D was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 26: Relative FcγRIIIa-F Binding Affinity



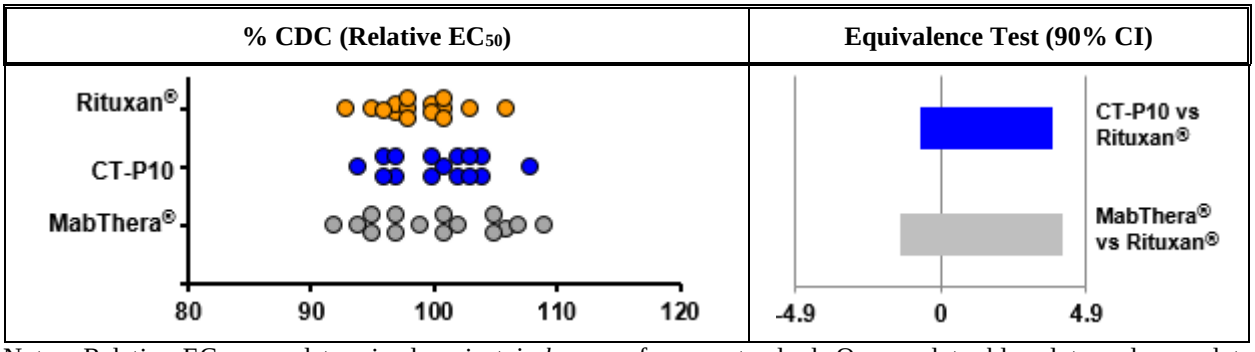
Notes: Relative K_D was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 27: Relative FcRn Binding Affinity

3.2.2.3 Fab- and Fc-mediated Binding

Complement-Dependent Cytotoxicity (CDC)

The Fc portion of IgG1 antibodies can interact with soluble C1q, initiating the classical complement pathway and resulting in lysis of the antibody-bound cell. Complement-dependent cytotoxicity was assessed using the B lymphoblast cell line, WIL2-S. Statistical analyses using the Tier 1 (equivalence test) approach showed that CT-P10, Rituxan® and MabThera® are statistically equivalent, with highly similar CDC potency. The data are shown in Figure 28 with a scatter plot on the left and equivalence test on the right. On the right of Figure 28, the equivalence margin of Rituxan® is shown by vertical solid lines with the numerical values of the equivalence margin at the bottom, and the confidence interval of mean difference for CT-P10 and MabThera® are depicted by horizontal bars.

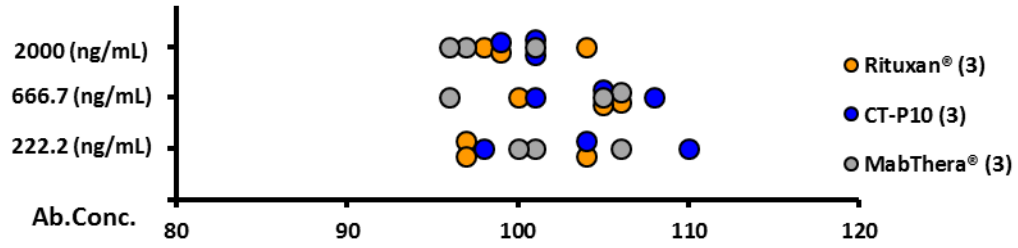
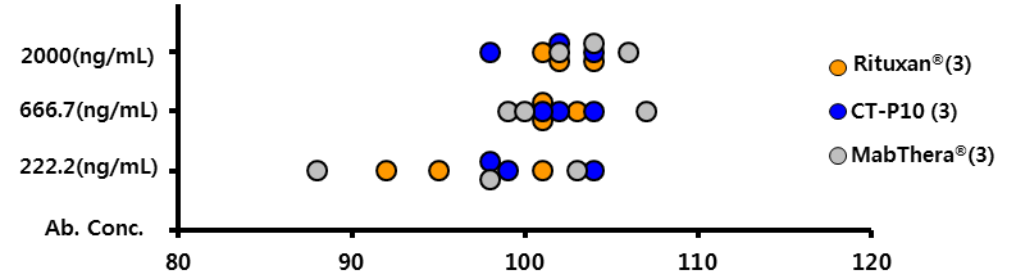
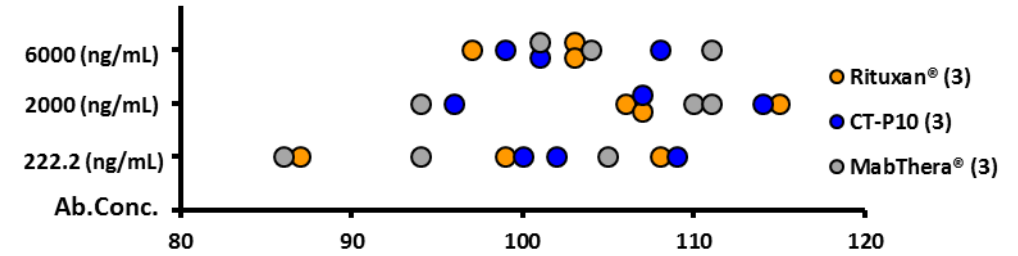


Notes: Relative EC_{50} was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The 90% CI of the mean difference between the 2 products (blue or grey bars) was required to be within the equivalence margin (±1.5 σ_R of Rituxan® lots, grey lines) to meet the equivalence acceptance criteria.

Figure 28: Relative CDC of WIL2-S Cells and Equivalence Test Results

To confirm similarity and to support extrapolation to the Proposed Indications (Section 1.1), CDC was evaluated using B-cells purified from PBMC of a healthy donor, a NHL patient and a CLL patient.

CT-P10, Rituxan® and MabThera® induced similar CDC potency in these assays conducted at 3 antibody concentrations (Figure 29), illustrating the comparable functional activity of the 3 products using B-cells from the PBMC of individuals of different disease state.

B-cell Donor	% CDC (Relative EC_{50})
Healthy donor	
NHL patient	
CLL patient	

Notes: Relative EC_{50} was determined against CT-P10 *in-house* reference standard. Statistical analysis was not performed due to the limited number of lots. Number of lots used in the additional study is indicated in brackets. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 29: Relative CDC of B-cells from a Healthy Donor, NHL Patient and CLL Patient at Multiple Antibody Concentrations

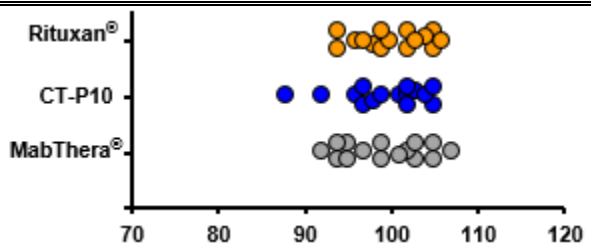
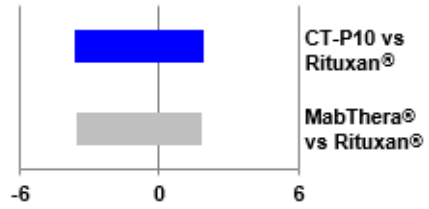
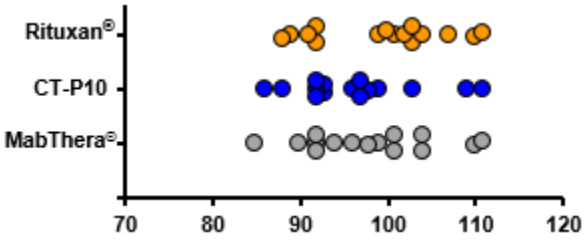
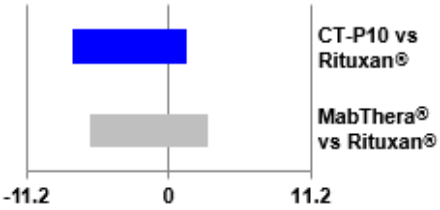
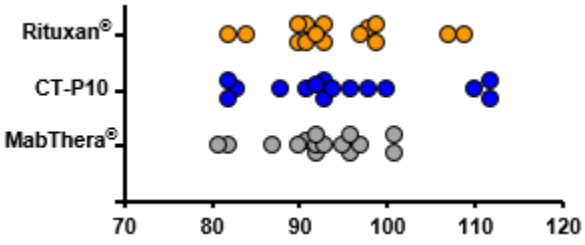
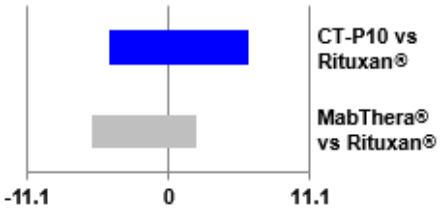
Antibody-Dependent Cellular Cytotoxicity (ADCC)

ADCC is part of the innate immune system by which Fc-receptor-bearing effector cells kill infected cells or tumor cells through a non-phagocytic process. For ADCC to occur, rituximab must bind to CD20 on a target cell (via the Fab region) and to an effector cell (via the Fc region). Effector cells that mediate ADCC include PBMCs that consist predominantly of NK cells, monocytes and polymorphonuclear cells that include granulocytes such as neutrophils, basophils and eosinophils (Ackerman & Nimmerjahn, 2014).

A classical ADCC assay with Raji target cells and healthy donor PBMCs of FcγRIIIa-V/F allotype as effector cells was used to compare the ADCC of CT-P10, Rituxan® and MabThera®. An ADCC reporter assay with Raji target cells and a Jurkat cell line expressing human FcγRIIIa-V allotype and nuclear factor of activated T-cell (NFAT)-induced luciferase was also used, to provide further assurance of the similarity in initiation of ADCC.

ADCC using PBMC

Data from ADCC assays conducted at 3 concentrations were analyzed by equivalence test and showed that all 3 products are highly similar in ADCC. The 90% CIs of the mean difference between CT-P10 and Rituxan® and between MabThera® and Rituxan® were within the equivalence margin of Rituxan® (Figure 30).

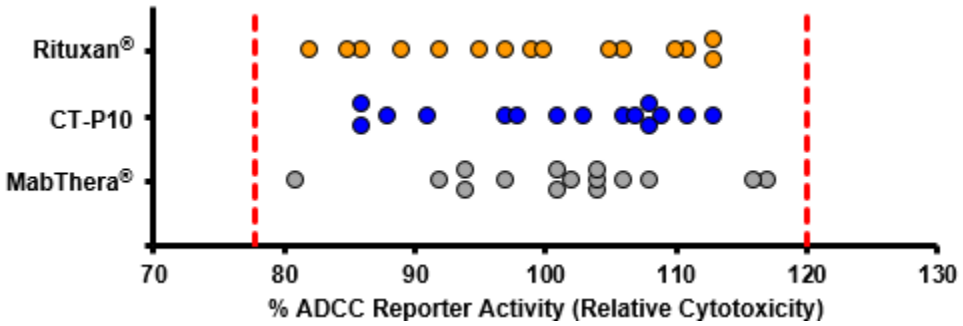
Ab. Conc.	% ADCC (Relative Cytotoxicity)	Equivalence Test (90% CI)
0.122 µg/mL		
0.035 µg/mL		
0.010 µg/mL		

Notes: Relative cytotoxicity was determined against CT-P10 *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The 90% CI of the mean difference between the 2 products (blue or grey bars) was required to be within the equivalence margin (±1.5 σ_R of Rituxan® lots, grey lines) to meet the equivalence acceptance criteria.

Figure 30: Relative ADCC of Raji Cells using PBMC (FcγRIIIa-V/F) Effector Cells and Equivalence Test Results

ADCC using Reporter Assay

Results from the ADCC FcγRIIIa-V reporter assay were consistent with those of the classical ADCC assay. Tier 2 analysis showed that all CT-P10 and MabThera® lots were within the quality range (mean ± 2SD) of Rituxan® in ADCC reporter activity and further support high similarity between CT-P10, Rituxan® and MabThera® in ADCC (Figure 31).

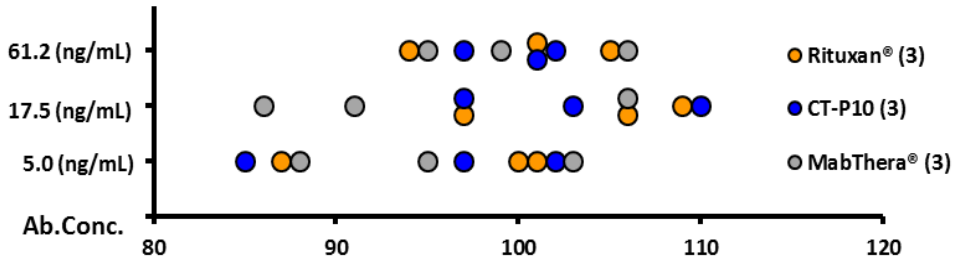
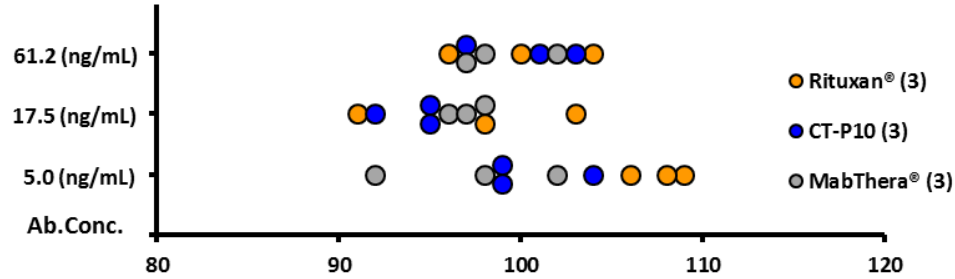
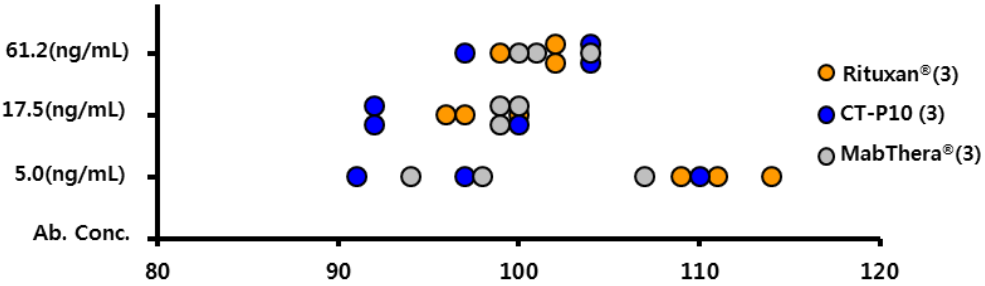


Notes: Relative cytotoxicity was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 2SD of the Rituxan® lots.

Figure 31: Relative ADCC using Reporter Assay (FcγRIIIa-V)

ADCC using PBMC from Different Patients

To confirm similarity and to support extrapolation to the Proposed Indications (Section 1.1), the classical ADCC assay was conducted with B-cells isolated from PBMC of a healthy donor, a NHL patient and a CLL patient as target cells. As shown in Figure 32, CT-P10, Rituxan® and MabThera® exhibited comparable ADCC regardless of target B-cell origin.

B-cell Donor	% ADCC (Relative Cytotoxicity) at Multiple Antibody Concentrations
Healthy donor	
NHL patient	
CLL patient	

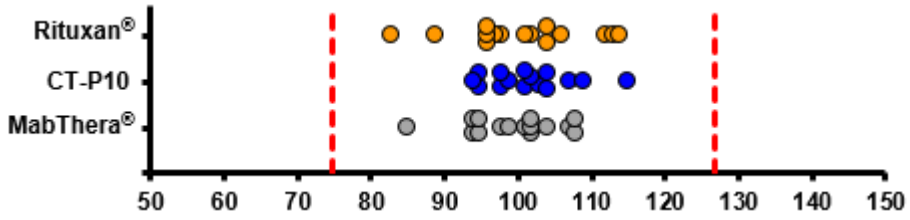
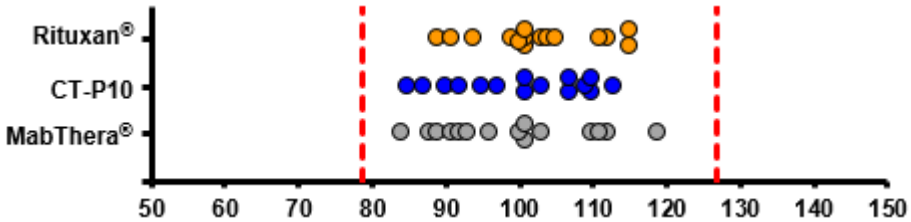
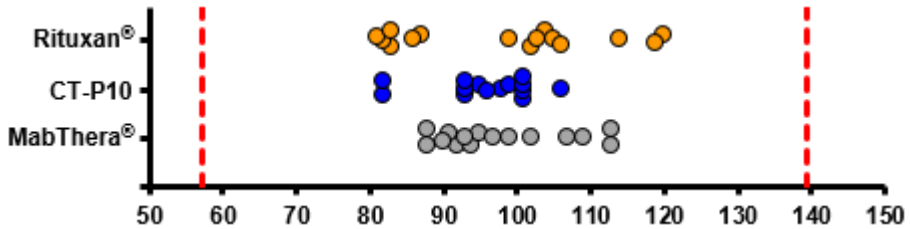
Notes: Relative cytotoxicity was determined against *in-house* reference standard. Statistical analysis was not performed due to the limited number of lots. Number of lots used in the additional study is indicated in brackets. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 32: Relative ADCC of B-cells from a Healthy Donor, NHL Patient and CLL Patient using Healthy Donor PBMC Effector Cells at Multiple Antibody Concentrations

Antibody-Dependent Cellular Phagocytosis (ADCP)

Antibody-dependent cell phagocytosis results in the destruction of cells targeted by a specific antibody via macrophage-mediated phagocytosis. Rituximab binding to CD20 expressing cells in the presence of effector cells (macrophages) may result in ADCP, which might contribute to the therapeutic effect of rituximab. Therefore, an ADCP assay was included in the similarity evaluation to provide assurance that all activities related to potential mechanisms of action were evaluated. ADCP was evaluated using primary monocyte-derived macrophages as effector cells and Raji cells as target cells using 3 concentrations of the 3 products.

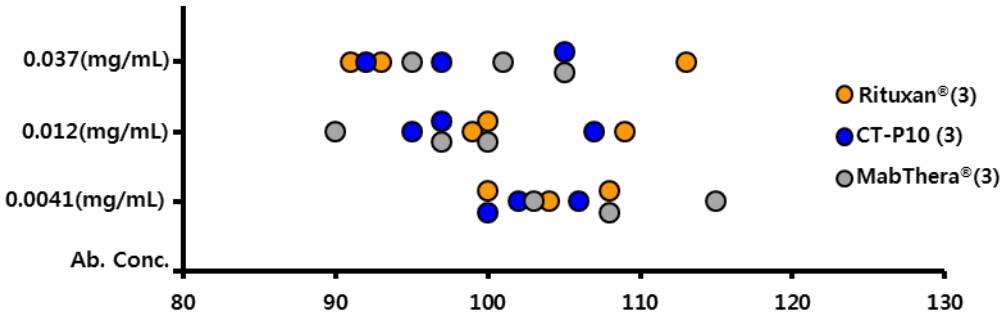
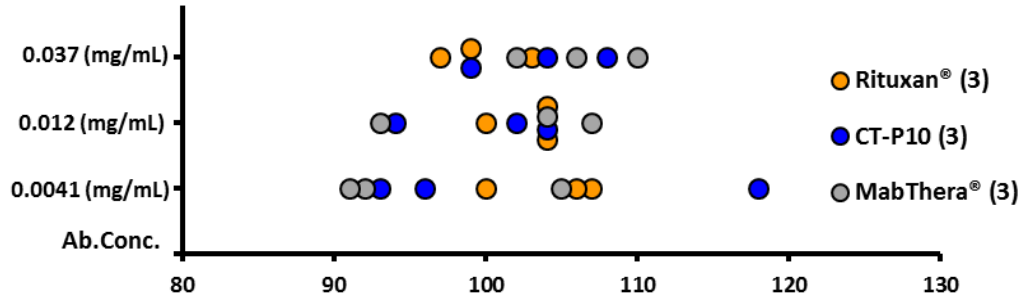
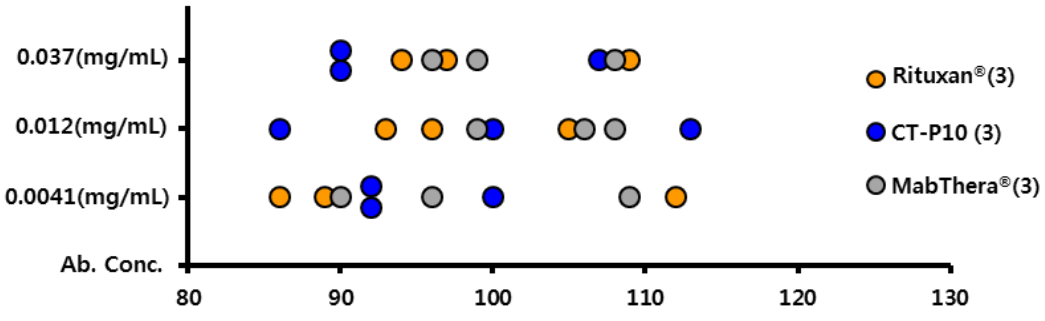
As shown in Figure 33, Tier 2 analysis demonstrated highly similar ADCP as all CT-P10 and MabThera® lots were within the quality range of Rituxan® (mean ± 3SD).

Ab. Conc.	% ADCP (Relative Phagocytosis)
25.0 ng/mL	
6.25 ng/mL	
1.56 ng/mL	

Notes: Relative phagocytosis was determined against *in-house* reference standard. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively. The dotted red lines represent the quality range limits based on mean ± 3SD of the Rituxan® lots.

Figure 33: Relative ADCP of Raji Cells using Primary Monocyte-derived Macrophage Effector Cells at Multiple Antibody Concentrations

To confirm similarity and to support extrapolation to the Proposed Indications (Section 1.1), ADCP analyses were performed in assays using primary monocyte-derived macrophages differentiated from healthy donor PBMCs as effector cells and target B-cells derived from the PBMC of a healthy donor, a NHL patient and a CLL patient. As shown in Figure 34, similar ADCP was observed for CT-P10, Rituxan® and MabThera® regardless of target B-cell origin.

B-cell Donor	% ADCP (Relative Phagocytosis) at Multiple Antibody Concentrations
Healthy donor	
NHL patient	
CLL patient	

Notes: Relative phagocytosis was determined against CT-P10 *in-house* reference standard. Statistical analysis was not performed due to the limited number of lots. Number of lots used in the additional study is indicated in brackets. Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 34: Relative ADCP of B-cells from a Healthy Donor, NHL Patient and CLL Patient using Primary Monocyte-derived Macrophage Effector Cells at Multiple Antibody Concentrations

3.3 Analytical Similarity Conclusion

The analytical similarity assessment demonstrated that CT-P10 is highly similar to Rituxan® and MabThera® in physicochemical structure, and in biological functions. The data have also shown that rituximab, commercialized as Rituxan® in the US, and as MabThera® in the EU, are comparable in physicochemical structure and biological functions, providing the analytic component of the scientific bridge between Rituxan® and MabThera®, justifying the relevance of data from comparative non-clinical studies of CT-P10 and MabThera®. The functional assays clearly demonstrate that CT-P10 is highly similar to Rituxan® and MabThera® in activities related to MoA, to the extent the MoA of Rituxan® are known, supporting a conclusion that there are no clinically meaningful differences between CT-P10, Rituxan® and MabThera® in biological function.

These analytical similarity studies also support extrapolation to the Proposed Indications (Section 1.1). Firstly, the similarity of CT-P10 to Rituxan® and MabThera® established by extensive physicochemical and structural characterization confirmed the absence of physicochemical or structural differences that could have significant clinical impact. Secondly, CT-P10, Rituxan® and MabThera®, were highly similar in activities related to the known and putative mechanisms of action. Finally, CT-P10, Rituxan® and MabThera® had similar functional activities using primary human B-cells from individuals of different disease state. These data suggest that CT-P10 and Rituxan® can be expected to exert the same therapeutic effect as Rituxan® in the Proposed Indications, supporting extrapolation to the Proposed Indications (Section 1.1).

4 NON-CLINICAL SIMILARITY

4.1 Overview of Non-clinical Studies

The non-clinical program, designed in compliance with the FDA guidance on biotechnology and biosimilar products, consists of a human tissue binding (immunohistochemistry) study and an *in vivo* comparative pharmacology and toxicology study in cynomolgus monkeys (Table 7). The objective of these studies was to confirm that CT-P10 and MabThera® have similar pharmacologic and safety profiles. The findings from these studies are also supported by the *in vitro* pharmacodynamic similarity results obtained in the analytical program (Section 3.2.2).

The studies fulfill the statutory requirement for "animal studies including an assessment of toxicity" and support the similarity of CT-P10 and MabThera®. As an analytic bridge was established between EU-approved MabThera® and US-licensed Rituxan® (Section 3.2), the results of these studies support the conclusion that CT-P10 is similar to MabThera®, and by extension, to Rituxan®.

Table 7: Non-clinical Similarity Studies using CT-P10 and MabThera®

Type of Study	Species	Treatment Administration	Duration of Dosing	Dose	Objective
CT-P10 Tissue Binding Study	Human tissues	N/A	N/A	N/A	Compare CT-P10 to MabThera® with respect to PD
CT-P10 8-week Repeat-Dose Toxicity Study	Cynomolgus monkeys (3 males and 3 females in each group)	Intravenous (bolus) administration	Weekly for 8 weeks	20 mg/kg of CT-P10 or MabThera® once a week	Compare CT-P10 to MabThera® with respect to PD, toxicokinetics, toxicity, and injection site reactions

4.2 Non-clinical Pharmacodynamics

Tissue binding of CT-P10 and MabThera® was assessed in a panel of human tissues. The primary PD effect on germinal center development in mesenteric lymph nodes and spleen were studied *in vivo* in the 8-week repeat toxicity study in cynomolgus monkeys. The results are summarized in Table 8.

Table 8: Pharmacodynamic Similarity Results for CT-P10 and MabThera®

Study	Key Findings
Human Tissue Binding & *In Vivo* Effect on B-cell in the Cynomolgus Monkey	
CT-P10: Human Tissue Binding Study	The pattern of binding to lymphoid organs, staining profile and intensity were similar for CT-P10 and MabThera®.
CT-P10: 8-Week Repeat-Dose Toxicity Study in Cynomolgus Monkeys	The pattern of B-cell depletion in peripheral blood, spleen, lymphatic nodes and bone marrow was consistent between CT-P10 and MabThera®. Decreased germinal center development was seen in the mesenteric lymph nodes and spleens in both CT-P10 and MabThera® groups.

4.3 Non-clinical Toxicokinetics

Since the CT-P10 formulation is for intravenous use, an absorption study was not necessary. The 8-week repeat-dose toxicity study in cynomolgus monkeys was conducted to evaluate the toxicokinetic (TK) exposure profiles of CT-P10 and MabThera®.

C_{max} and the extent of systemic exposure (AUC_{0-168}) of cynomolgus monkeys were determined following a weekly dose of 20 mg/kg/week of CT-P10 or MabThera®. CT-P10 and MabThera® groups had similar concentration-time profiles and TK parameters.

TK profiles on Day 22 were analyzed using data from a small number of animals due to exclusion of animals having ADA. The number of animals in the CT-P10 group and MabThera® group with ADA were comparable, and the same number of animals in each group had NAb. Thus, the *in vivo* immunogenic potential of CT-P10 and MabThera® was deemed to be similar.

4.4 Non-clinical Toxicology

The safety profiles of CT-P10 and MabThera® were similar over the 8-week repeat-dose toxicity study in cynomolgus monkeys. The results from general toxicity and local tolerance evaluations were consistent between CT-P10 and MabThera®. A summary of the toxicology study findings is provided in Table 9.

Table 9: Toxicology Similarity Study Results (CT-P10 and MabThera®)

Evaluation	Key Findings
Repeat-dose Toxicity	CT-P10 produced no adverse toxicological findings in cynomolgus monkeys. With the exception of 2 deaths in animals receiving MabThera®, the monkeys responded to CT-P10 and MabThera® treatment in a similar manner.
Local Tolerance at Injection Sites	There were no significant differences in injection site findings between CT-P10 and MabThera®.

4.5 Conclusion

The comparative tissue binding and the *in vivo* repeat-dose study evaluating toxicity and TK showed similarity between CT-P10 and MabThera®. Based on the high analytic similarity between MabThera® and Rituxan®, the non-clinical pharmacology, toxicokinetic and toxicology data support the conclusion that CT-P10 is similar to MabThera®, and by extension, to Rituxan®. Thus, these studies contribute to the totality of evidence showing CT-P10 is biosimilar to Rituxan® in the Proposed Indications (Section 1.1).

5 CLINICAL SIMILARITY

Table 10: Overview of the Clinical Similarity Data in CT-P10 Development Program[5]

PK similarity	• In PK Subset of Study CT-P10 3.3 with treatment-naïve advanced FL patients, the PK similarity (CT-P10 to Rituxan®) has been demonstrated for both AUC_{tau} and $C_{max,ss}$ during Cycle 4 (9-12 weeks) of treatment with the pre-defined equivalence margin of 80% - 125% with all available concentrations in PK population receiving all of the first 4 doses (full) of rituximab (Section 5.2.1.1). • The PK similarity (CT-P10 to Rituxan®) has been supported by the secondary PK endpoints (C_{max} and C_{trough} at each dose) over 7 months in Study CT-P10 3.4 with patients with treatment-naïve low tumour burden follicular lymphoma (LTBFL) (Section 5.2.1.2). • In PK Subset of Study CT-P10 3.2 with RA patients, 3-way PK similarity (CT-P10 to Rituxan®, CT-P10 to MabThera®, MabThera® to Rituxan®) has been demonstrated for all primary PK endpoints ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} over the first 24 weeks) contained within the pre-defined PK similarity margin of 80% - 125% with all available concentrations from the analysis population receiving a total dose of 2,000 mg of rituximab (Section 5.2.1.3). • PK similarity of CT-P10 to MabThera® has been also demonstrated in Study CT-P10 1.1 in RA patients.
PD similarity	• In Studies CT-P10 3.4 (LTBFL) and CT-P10 3.3 (advanced FL), similarity of B-cell depletion between CT-P10 and Rituxan® has been convincingly demonstrated (Section 5.2.2).
Efficacy similarity	• In Study CT-P10 3.4 with treatment-naïve LTBFL patients, therapeutic equivalence for the ORR over 7 months has been demonstrated within the pre-specified equivalence margin of ±17% agreed with the FDA (Section 5.3.1.3). • In Study CT-P10 3.3 in treatment-naïve advanced FL patients, therapeutic non-inferiority of CT-P10 to Rituxan® has been demonstrated for the ORR over 8 cycles (24 weeks) of the R-CVP induction period according to the 1999 IWG criteria. In addition, duration of response (CR, CRu or PR) and comparable survival results (PFS and OS) were documented during monotherapy maintenance period further supporting the efficacy similarity of CT-P10 to Rituxan® in FL patients (Section 5.3.2.3 and Section 5.3.2.4).

[5] The clinical studies are intended solely to satisfy the statutory requirements for the licensure of a biosimilar and are not intended to encourage the use of CT-P10 in any indication not included in CELLTRION's draft label submitted with its May 29, 2018 351(k) BLA resubmission.

Comparison of safety	• With a total of 398 FL patients treated with CT-P10 and Rituxan® to date in the CT-P10 clinical development program, the type and incidence of adverse events (AEs), fatal AEs, grade ≥3 AEs, serious adverse events (SAEs), adverse events of special interest (AESI), and AEs leading to permanent study drug discontinuation were comparable between the treatment groups across all CT-P10 studies and in line with safety characteristics reported in the USPI of Rituxan® (2018) (Section 5.4.1.1). • Long-term safety data for a median follow-up duration of 22.6 months from advanced FL patients (Study CT-P10 3.3) were in line with the safety profile of Rituxan®. Safety data over 7 months for LTBFL patients (Study CT-P10 3.4) were also in line with the safety profile of Rituxan®. • In ongoing studies in FL patients (Studies CT-P10 3.3 and CT-P10 3.4), no new safety issues have been identified and available data up to date indicates that the safety profile of CT-P10 is comparable to that of Rituxan® in the NHL population. • Fourteen (14) deaths were reported in the CT-P10 FL studies. All cases were thoroughly investigated by CELLTRION and presented in details in Section 5.4.1.4. • The pattern of AESIs (infections, infusion related reactions, anaphylaxis and progressive multifocal leukoencephalopathy [PML]) reported in the studies comparing the safety of CT-P10 and the reference products was consistent with the well-known safety profile of Rituxan®. There were no cases of PML reported in the program. Through the comparison with the safety profile of Rituxan® described in the USPI (2018), published literature and the safety database, it was concluded that the safety profile of CT-P10 mirrors that of Rituxan® (Section 5.4.1.7).
Immunogenicity similarity	• The immunogenicity profile in terms of both ADA and NAb was similar between CT-P10 and Rituxan® during the induction period and maintenance period in advanced FL patients, over 7 months in LTBFL patients and between CT-P10 and Rituxan®/MabThera® up to 48 weeks in RA patients (Section 5.4.2). • No discernible differences in the immunogenicity profile were observed in the patients who 1) switched from either Rituxan® or MabThera® to CT-P10, 2) maintained on CT-P10 treatment, or 3) maintained on Rituxan® treatment up to 72 weeks in Study CT-P10 3.2 (RA patients) (Section 5.4.2.3). • From the assessment on the impact of ADA present on PK, efficacy and safety, it was concluded that emergence of ADA was not associated with worsening of clinical outcomes or with an increased risk of reactions to subsequent infusions which is in line with the observation in the reference products. Importantly, the impact of ADA formation on drug exposure, ORR and frequencies of IRRs was similar between CT-P10 and reference products (Section 5.4.2.5).

Abbreviations: ADA, Anti-drug antibody; AE, Adverse event; AESI, Adverse event of special interest; advanced FL, advanced follicular lymphoma; $AUC_{0\text{-inf}}$, Area under the serum concentration-time curve from time zero to infinity; $AUC_{0\text{-last}}$, Area under the concentration time curve from time zero to time of last quantifiable concentration; AUC_{tau}, Area under the serum concentration-time curve at steady state; C_{max}, Maximum serum concentration; $C_{max,ss}$, Maximum serum concentration at steady state; C_{trough}, Trough serum concentration; CR, Complete response; CRu, Unconfirmed complete response; FDA, Food and Drug Administration; IWG, International Working Group; IRR, Infusion related reaction; LTBFL, low tumor burden follicular lymphoma; NAb, Neutralizing antibody; NHL, Non–Hodgkin's lymphoma; ORR, Overall response rate; OS, Overall survival; PD, Pharmacodynamics; PFS, Progression free survival; PK, Pharmacokinetics; PML, Progressive multifocal leukoencephalopathy; PR, Partial response; RA, Rheumatoid arthritis; R-CVP, Rituximab, Cyclophosphamide, Vincristine, and Prednisone; SAE, Serious adverse event; USPI, United States prescribing information.

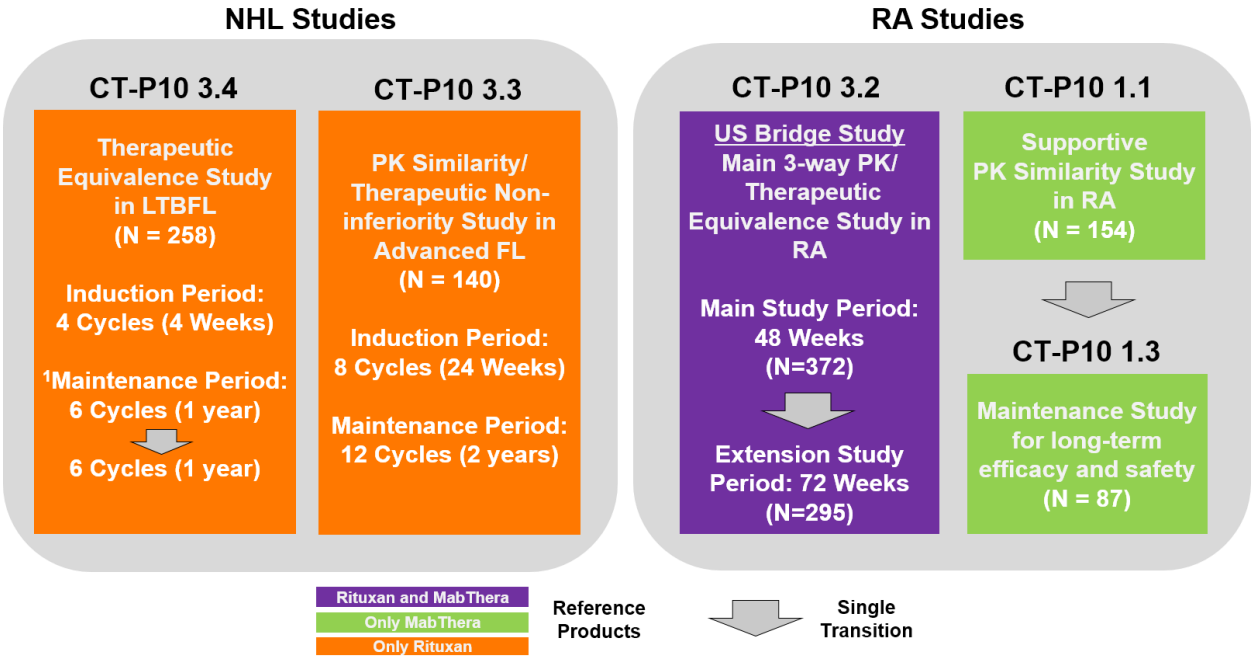
5.1 Overview of Clinical Development Program

The CT-P10 clinical program was developed in consultation with the FDA and the EMA to support the global development of the product and included 258 patients with LTBFL, 140 patients with advanced FL and 526 patients with RA. The development program includes 2 ongoing studies in patients with LTBFL and advanced FL (Study CT-P10 3.4 and Study CT-P10 3.3, respectively) and 3 completed studies in patients with RA (Studies CT-P10 3.2, CT-P10 1.1 and CT-P10 1.3) as shown in Figure 35 and Table 11. For Study CT-P10 3.4, the primary efficacy endpoint and additional PK, safety and immunogenicity data over 7 months are available. For Study CT-P10 3.3, primary endpoint results (i.e., PK at Cycle 4 and efficacy over 8 cycles) and additional efficacy and safety results including the maintenance period (with a median follow-up duration of 22.6 months) are available.

All three RA studies: CT-P10 3.2, CT-P10 1.1 and its open-label extension CT-P10 1.3 were completed. As clinical similarity between CT-P10 and Rituxan is primarily supported by the studies in FL patients, only PK similarity and immunogenicity results from RA studies are discussed.

The comparative clinical studies in patients with LTBFL and advanced FL provide clinical data to support the extrapolation of clinical similarity to the Proposed Indications for CT-P10 (Section 1.1).

Together, the 5 studies provide comparative clinical data to demonstrate that no clinically meaningful differences between CT-P10 and Rituxan® exist and to fulfill the FDA requirements for the demonstration of biosimilarity for the Proposed Indications (Section 1.1).



[1]A single transition from Rituxan® to CT-P10 after 1 year maintenance period to assess the safety profile.

Figure 35: Overview of the CT-P10 Clinical Development

Table 11: CT-P10 Studies Submitted for BLA

Study	Study Population	Reference Product	Objectives	Study Duration	Primary Endpoints
Pivotal FL Studies (Ongoing)					
CT-P10 3.4	Treatment naïve LTBFL (N=258)	Rituxan®	Efficacy and Safety	At least 27 months (Data over 7 months are included)	ORR (CR+CRu+PR) over 7 months
CT-P10 3.3	Treatment naïve advanced FL (N=140)	Rituxan®	PK, Efficacy and Safety	At least 3 years (Data with median follow-up of 22.6 months are included)	Part 1 (PK Subset): AUC_{tau}, $C_{max,ss}$ at Cycle 4 Part 2 (Full Set): ORR (CR+CRu+PR) over 8 cycles
Supportive RA Studies (Completed)					
CT-P10 3.2	Moderate -to severe RA refractory to TNFi (N=372)	Rituxan® and MabThera®	PK, Efficacy, Safety and Immunogenicity	72 weeks	Part1 (PK Subset): $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, C_{max} over 24 weeks Part2 (Full Set): DAS28 (CRP) at Week 24
CT-P10 1.1	Moderate -to severe RA refractory to TNFi RA (N=154)	MabThera®	PK, Efficacy, Safety and Immunogenicity	48 weeks	$AUC_{0\text{-}last}$, C_{max} over 24 weeks
CT-P10 1.3 (Extension study of CT-P10 1.1)	Moderate -to severe RA refractory to TNFi (N=87)	Not applicable	Long term efficacy, safety and immunogenicity	96 weeks (including CT-P10 1.1)	-

Abbreviations: $AUC_{0\text{-}inf}$, Area under the serum concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, Area under the concentration-time curve from time zero to time of last quantifiable concentration; AUC_{tau}, Area under the concentration-time curve at steady state; BLA, Biologics License Application; C_{max}, Maximum serum concentration; $C_{max,ss}$, Maximum serum concentration at steady state; CR, Complete response; CRP, C-Reactive protein; CRu, Unconfirmed complete response; DAS28, Disease activity score using 28 joint counts; FL, Follicular lymphoma; LTBFL, Low tumor burden follicular lymphoma; ORR, Overall response rate; PK, Pharmacokinetics; PR, Partial response; RA, Rheumatoid arthritis; TNFi, Tumor necrosis factor inhibitors.

5.1.1 Rationale for Study Populations and Designs

The choice of patient populations in CT-P10 clinical studies was guided by the FDA and the EMA advice for selecting most homogenous and sensitive conditions of use in which to detect potential differences between CT-P10 and Rituxan®.

The choice of ORR as a primary endpoint for comparative efficacy evaluation in FL studies has been recommended and endorsed by the FDA and the EMA. The equivalence approach for comparison of ORR in Study CT-P10 3.4 (LTBFL) and non-inferiority approach to compare ORR in Study CT-P10 3.3 (advanced FL) are in line with the FDA's guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (2015). The design of the studies was scientifically justified as follows:

The FDA recommended that patients with treatment-naïve LTBFL should be used for the pivotal comparative efficacy study in order to demonstrate that there are no clinically meaningful differences between CT-P10 and Rituxan®. The choice of patients with LTBFL (Study CT-P10 3.4) and rituximab monotherapy to establish clinical similarity in the Proposed Indications (Section 1.1) is supported by the following:

- The use of monotherapy in treatment-naïve LTBFL settings eliminates the potential impact of chemotherapy in the assessment of efficacy, PK/PD, safety and immunogenicity.
- The effect size is sufficiently large in LTBFL patients, allowing for the detection of clinically meaningful differences between a biosimilar and a reference product in a comparative efficacy study. A large effect size for ORR was observed in Ardeshna *et al*. (2014) study.
- Rituximab, as a first-line single-agent therapy for previously untreated patients with indolent NHL including LTBFL, has been highly active and well tolerated and is an accepted treatment modality in FL (NCCN, 2018).
- Single-agent rituximab treatment, consisting of rituximab induction and rituximab maintenance (rituximab 375 mg/m^2 weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years), led to a significant increase of the time to commencement of the new treatment and higher improvements in quality of life (QoL) compared to watchful waiting (Ardeshna *et al.*, 2014).
- As tumor burden, B-cell microenvironment, and Fc receptor binding may impact response, LTBFL is sensitive in detecting any potential clinically meaningful differences in therapeutic effect.

The EMA recommended to use advanced FL for the comparative PK and efficacy assessment. The choice of patients with previously untreated advanced FL and background CVP regimen (Study CT-P10 3.3) to establish clinical similarity in the Proposed Indications (Section 1.1) is supported by the following:

- Patients with advanced FL are representative of the target oncology population(s), and rituximab (R)-chemotherapy regimens are still utilized frequently in the US (Nooka *et al.*, 2013).
- The chemotherapy regimen, CVP, used for Study CT-P10 3.3 can provide sufficient assay sensitivity for comparison between CT-P10 and Rituxan® in terms of PK, efficacy and safety. The CVP regimen is a relatively modest chemotherapy regimen in terms of its ORR effect compared with others such as cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisone (CHOP) regimen. Therefore, CVP can serve better as a background chemotherapy regimen such that the assessment of clinical similarity can be more readily carried out.
- The addition of rituximab to CVP does have a significant incremental effect with an increase in the treatment response (ORR) in previously untreated patients with advanced FL (Marcus *et al.*, 2005). Thus, this model provides adequate assay sensitivity.
- The recommended treatment for advanced FL involves the use of rituximab in combination with chemotherapy followed by rituximab maintenance therapy. Patients in Study CT-P10 3.3 are treated with monotherapy after the 8-cycle induction therapy, allowing to obtain an additional supportive efficacy and safety data during monotherapy treatment without any potentially confounding effect of CVP.

In addition, the choice of patients with moderate-to-severely active RA (Study CT-P10 3.2) to generate PK similarity and immunogenicity data for the licensure of CT-P10 for the Proposed Indications (Section 1.1) is justified by the following:

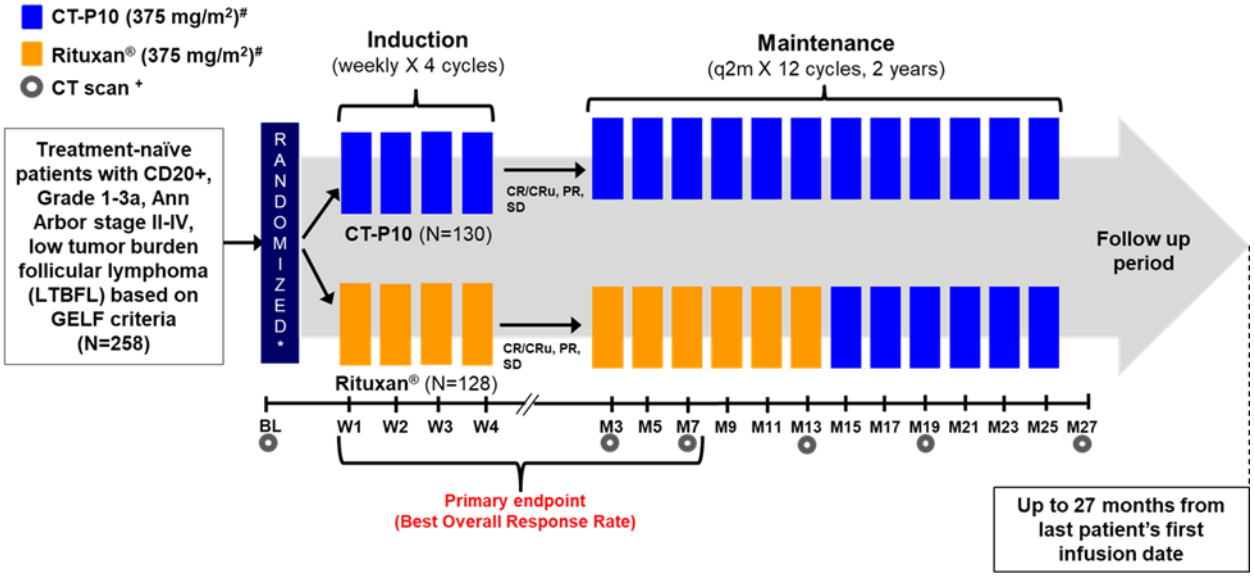
- The RA population is relatively homogeneous compared to lymphoma and GPA/ MPA populations, which are characterized by high variation in disease states, comorbidities, disease heterogeneity which may confound the assessment of PK similarity.
- When assessing the comparability of the immunogenicity profile between agents, RA is considered a more sensitive model than NHL or CLL because a higher rate of anti-drug antibody formation has been reported in the RA population.

In order to demonstrate clinical similarity between CT-P10 and Rituxan® in the Proposed Indications (Section 1.1), the eligibility criteria in LTBFL, advanced FL and RA studies carefully considered and were consistent with respective characteristics of patient populations included in historical studies recommended and agreed with the FDA and the EMA.

5.1.2 Study CT-P10 3.4 in Patients with Low Tumor Burden Follicular Lymphoma (LTBFL)

Study CT-P10 3.4 is a Phase 3, randomized, active-controlled, double-blind study designed to compare efficacy and safety between CT-P10 and Rituxan® in treatment-naïve patients with Grade

1 to Grade 3a, Ann Arbor stage II-IV, LTBFL based on Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria (Solal-Céligny *et al.*, 1998) by demonstrating the therapeutic equivalence in the monotherapy setting. The study consisted of an induction period with weekly administration of the study drug followed by a maintenance period, which included up to 12 cycles, administered 2 months apart. While this study is ongoing, results over 7 months from Day 1 of Cycle 1, including induction period (weekly, 4 cycles) and 2 cycles of maintenance period (2-monthly), which includes primary efficacy and other analyses, were submitted in the BLA. The schematic outline of the study is illustrated in Figure 36.



Premedication (antipyretic, antihistamine, glucocorticoid)
* Stratified by region (Asia Pacific vs. Europe vs. North America and other), Stage (II vs. III vs. IV), and age (≥60 vs. <60 years)
+ CT scan will be also performed every 6 months during follow-up period.
Abbreviations: BL, Baseline; CR, Complete Response; CRu, Unconfirmed Complete Response; GELF, Groupe d'Etudes des Lymphomes Folliculaires; LTBFL, Low Tumor Burden Follicular Lymphoma; M, Month; q2m, Every 2 months; SD, Stable Disease; PR, Partial Response; W, Week
Note: CT-P10 or Rituxan® (375 mg/m^2 IV) monotherapy was administered every week for 4 weeks in the induction period. During the maintenance period, CT-P10 or Rituxan® (375 mg/m^2 IV) monotherapy was administered every 2 months up to 12 cycles (up to 6 infusions of randomized product followed by up to 6 infusions of CT-P10) over 2 years until disease progression in patients who had disease control during the induction period.

Figure 36: Design of the Study CT-P10 3.4

As agreed with the FDA, the primary efficacy endpoint for evaluation of therapeutic equivalence was overall response rate: ORR (complete response [CR] + unconfirmed complete response [CRu] + partial response [PR]) for CT-P10 and Rituxan® over 7 months, which included completed induction period (weekly, 4 cycles) and 2 cycles of maintenance period (2-monthly) (last patient last visit: January 04, 2018). The best overall response is calculated from the best responses recorded for individual patients throughout the 7 months treatment period.

ORR measurements were based on tumor assessments using computed tomography (CT) with or without magnetic resonance imaging (MRI) scans, which were performed at screening and regular

intervals during the study. The tumor assessments were performed at baseline, Month 3, Month 7, Month 13, Month 19 and Month 27 from randomization; and every 6 months during the follow-up period until treatment with new anticancer therapy or disease progression occurs. For all post-baseline assessments, the scan modality was the same as that used at baseline. The tumor assessments were reviewed by independent, centralized reviewers who were blinded to treatment.

In addition, a number of secondary efficacy assessments will be performed upon study completion including ORR during the study period, PFS, time-to-progression and OS.

The analysis of other objectives of the study included comparative assessment of PK, PD, safety and immunogenicity over 7 months.

5.1.2.1 Key Inclusion/Exclusion Criteria

Study CT-P10 3.4 enrolled patients with LTBFL based on the GELF criteria (Solal-Céligny *et al.*, 1998) according to the following criteria:

Inclusion Criteria

- 18 years or older
- Histologically confirmed CD20+ FL grades 1 to 3a
- At least 1 measurable tumor mass
- Ann Arbor stage II, III or IV
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1
- Patient has low tumour burden, defined as based on GELF criteria:
    - No B symptoms,
    - LDH < upper limit of normal (ULN),
    - Largest nodal or extra mass <7 cm,
    - <3 nodal sites with a diameter ≥3 cm,
    - No significant serous effusions detectable clinically or on CT (small, clinically non-evident effusions on CT scan are not deemed significant),
    - Spleen ≤16 cm by CT, and
    - No clinical organ failure or organ compression (e.g., ureteric obstruction)
- Adequate bone marrow, hepatic, and renal function reserve:
    - Hemoglobin level of ≥10 g/dL,
    - Absolute neutrophil count (ANC) of ≥1,500/mm^3, and
    - Platelet count of ≥100,000/mm^3

Exclusion Criteria

- Prior treatment for non-Hodgkin’s lymphoma

- Evidence of histological transformation to high-grade or diffuse large B-cell lymphoma

A complete list of inclusion and exclusion criteria for the study is provided in Appendix 4.

5.1.2.2 Randomization and Treatment

A total of 258 male and female patients with LTBFL were enrolled in Study CT-P10 3.4. Patients were randomized in a 1:1 ratio to receive either CT-P10 or Rituxan® (375 mg/m^2 weekly).

Randomization was stratified by region (Asia Pacific vs. Europe vs. North America and other), stage (II vs. III vs. IV) and age (≥60 vs. <60 years).

Patients received CT-P10 or Rituxan® monotherapy treatment at a dose of 375 mg/m^2 weekly for 4 weeks in the induction period. For patients who achieve disease control (CR, CRu, PR or stable disease) after the induction period, CT-P10 or Rituxan® (375 mg/m^2 IV) will be administered every 2 months up to a maximum of 6 cycles for 1 year during the maintenance period. Subsequently, all patients will be allowed to receive CT-P10 every 2 months for 1 additional year.

Premedication consisting of an antipyretic (e.g., paracetamol), an antihistamine (e.g., H1 antihistamine), and a glucocorticoid (prednisone on Day 1) was administered 30 minutes before each infusion of CT-P10 or Rituxan®.

5.1.2.3 Statistical Analysis

Primary Endpoint and Margin Determination

As agreed with FDA, ORR (CR + CRu + PR) over 7 months has been selected as the primary endpoint in Study CT-P10 3.4. ORR was calculated as best overall response over 7 months and assessed by central review. While OS and PFS have been widely used as the primary endpoints in cancer clinical trials for innovative therapies, use of standard endpoints such as OS and PFS may be challenging due to high patient numbers and long treatment duration required for biosimilar cancer clinical trials. Use of surrogate markers generally reduces the number of patients and shortens the duration of the trial, thus, the surrogate endpoint, such as ORR, serves as a more realistic primary endpoint in biosimilar cancer clinical trials (Ahn & Lee, 2011). A previous study in LTBFL patients used ORR to assess the therapeutic effect of rituximab monotherapy and the magnitude of ORR difference was between 77-88% (Ardeshna *et al*., 2014), further justifying the sensitivity of this outcome measure in a comparative trial.

Ardeshna *et al.* (2014) was a randomized controlled study that investigated the effect of rituximab following induction with 4 weekly doses and maintenance with 2 cycles administered 2 months apart. Overall response was reported at 7 months. This study was most relevant for the Study CT-P10 3.4 in terms of the duration of exposure and timing for the primary endpoint assessment. Therefore, eligibility criteria for Study CT-P10 3.4 carefully considered population characteristics of Ardeshna *et al*. (2014) study.

The pre-specified equivalence margin for ORR was determined in agreement with FDA. For the analysis of the primary efficacy endpoint, ±17% was proposed as the therapeutic equivalence

margin. This margin was derived from the historically reported effect of rituximab and estimated based on the lower bound of the 95% CI of the difference between the ORR of patients in the maintenance group and the ORR of patients in the "watch-and-wait" group at 7 months in Ardeshna *et al.* (2014), as detailed below.

The equivalence margin of ±17% preserves at least 77% of the reported effect of rituximab based on the lower bound of the 95% exact CI (0.753) of the estimated difference between ORR of patients who received rituximab over a 7 month period (88%, 162/184) and ORR of patients in "watch-and-wait" group (6%, 9/155) (Ardeshna *et al.,* 2014). The estimated difference of ORRs was 82% (the difference between 88% and 6%) and its 95% exact CI was (75.3% to 87.5%), which was calculated by the exact binomial method. The historical treatment effect of rituximab for the equivalence is estimated conservatively as 75%. Therefore, the equivalence margin is proposed as ±17% by applying 77% preservation rate.

Sample Size

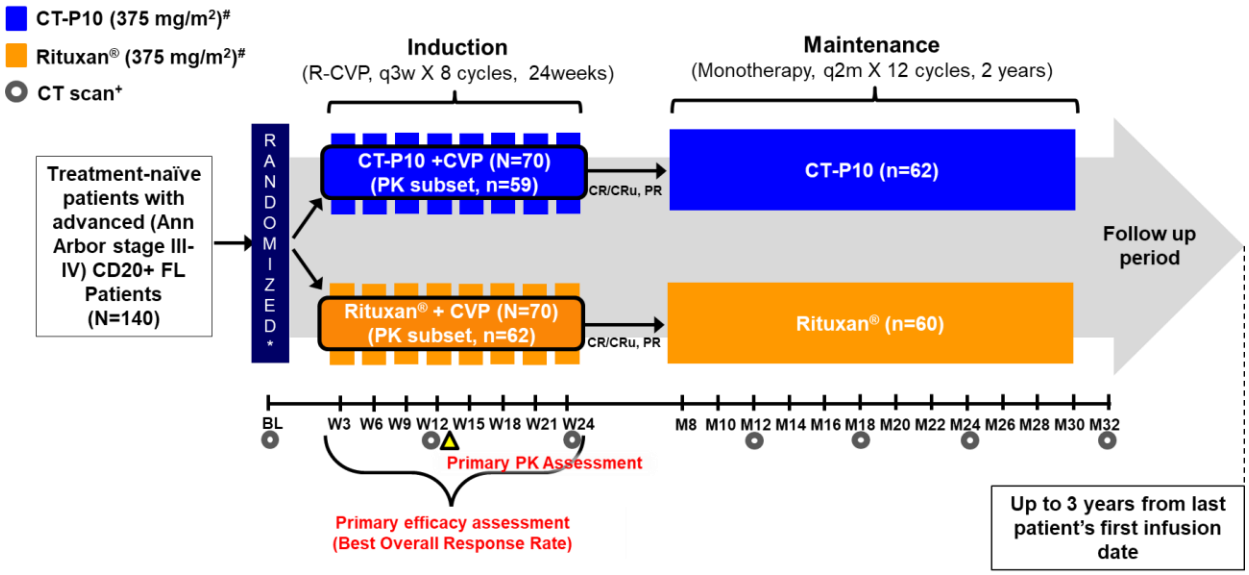
For the analysis of the primary efficacy endpoint (the proportion of patients with a CR, CRu, or PR response over 7 months), a sample size of 174 patients (87 patients in each treatment group of CT-P10 and Rituxan®) was determined to provide 91% statistical power for the demonstration of similarity at a 5% significance level. The ITT population was the primary analysis population for the efficacy analysis. A supportive analysis of the primary endpoint was conducted using the Per-Protocol (PP) population. With a 13% drop-out rate, the PP population, was expected to provide 86% statistical power.

A blinded sample size re-assessment was pre-specified in order to adjust the study power in the event that the drop-out rates were greater than anticipated or the observed blinded ORR were lower than anticipated. Following the blinded reassessment (evaluable patients: 102/174 [53.7%]), an increase in the total sample size to at least 238 patients or up to 250 patients was recommended by the Data Safety Monitoring Board (DSMB) in order to achieve adequate statistical power. After the completion of patient enrolment, a total of 258 patients were randomized, satisfying the minimum statistical power pre-specified in the protocol. The adjustment made to the sample size had been confirmed in advance with the FDA.

5.1.3 Study CT-P10 3.3 in Patients with Advanced Follicular Lymphoma

Study CT-P10 3.3 is a Phase 1/3, randomized, active-controlled, double-blind study designed to demonstrate the PK similarity and non-inferiority of CT-P10 in comparison to Rituxan®, each administered in combination with CVP in treatment naïve patients with advanced (Ann Arbor stage III-IV) CD20+ FL. This study was designed in agreement with the EMA.

This study included a Part 1 that assessed PK in a subset of the total study population and a Part 2 that assessed efficacy in the total study population (PK Subset included). While this study is ongoing, the results from the 8 cycles (24 weeks) of the induction period and additional monotherapy maintenance period (by clinical cut-off date of July 31, 2017, including median follow-up data of 22.6 months and monotherapy maintenance period of ≥ 10 months) were submitted in the BLA. The schematic outline of the study is illustrated in Figure 37.



Premedication (antipyretic, antihistamine, glucocorticoid).
* Stratified by gender (male vs. female), FLIPI (0-2 vs. 3-5) and country.
+ CT scan will be also performed every 6 months during follow-up period.
Abbreviations: BL, Baseline; CD20+, Cluster of differentiation 20 positive; CR, Complete Response; CRu, Unconfirmed Complete Response; CT, Computed tomography; CVP, Cyclophosphamide, Vincristine, and Prednisone; FL, Follicular Lymphoma; M, Month; PK, Pharmacokinetics; PR, Partial Response; q2m, Every 2 months; q3w, Every 3 weeks; W, Week
Note: CT-P10 or Rituxan® (375 mg/m^2 IV) were co-administered with cyclophosphamide (750 mg/m^2 IV, Day 1 of each cycle), vincristine (1.4 mg/m^2 [up to a maximum of 2 mg] IV, Day 1 of each cycle), and prednisone (40 mg/m^2 oral, Day 1 to 5 of each cycle) every 3 weeks up to 8 cycles during the induction period. During the maintenance period, CT-P10 or Rituxan® (375 mg/m^2 IV) was administered alone every 2 months up to 12 cycles in patients who had a response during the induction period.

Figure 37: Design of the Study CT-P10 3.3

PK similarity assessment between CT-P10 and Rituxan® was conducted by evaluating AUC_{tau}, and $C_{max,ss}$ during Cycle 4 (Week 9-12), the time at which steady state rituximab levels are achieved based on historical Rituxan® PK studies in NHL patients (Jäger *et al*., 2012; Blasco *et al*., 2009; Berinstein *et al*., 1998). For the primary PK assessment at Cycle 4 in the induction period, samples were collected at pre-dose, end of infusion, 1 hour after the end of infusion, and were collected after the start of infusion for 24 hours, 168 hours, 336 hours, and 504 hours. Additional samples were collected on Day 1 of each cycle before administration (within 15 minutes prior to the study drug infusion) and at 1 hour after the end of study drug infusion of Cycles 1-3 and 5-8 of the induction period.

The co-primary efficacy endpoint for evaluation of non-inferiority was the ORR (CR + CRu + PR) over 8 cycles of CT-P10 or Rituxan®. The best overall response was calculated from the best responses recorded for individual patients over 8 cycles of the induction period. ORR measurements were based on tumor assessments conducted using CT or MRI scans, which were performed at screening and regular intervals during the study. The tumor assessments were set to be performed at screening and Week 12, Week 24 during the induction period; Month 12, Month 18, Month 24 and Month 32 during the maintenance period; and every 6 months during the

follow-up period. The tumor assessments were reviewed by independent, centralized reviewers who were blinded to treatment.

In addition, a number of secondary efficacy assessments were performed, including:

- Duration of response, defined as the time to first documentation of relapse or progression from the first time when criteria of response (CR, CRu or PR) is met;
- PFS, defined as the interval between randomization and disease progression, or death from any cause, whichever occurs first; and
- OS, defined as the interval between randomization and death from any cause.

The analysis of other objectives of the study included comparative assessment of PK, PD, safety and immunogenicity data with median follow-up of 22.6 months are included.

5.1.3.1 Key Inclusion/Exclusion Criteria

Study CT-P10 3.3 included patients with previously untreated advanced FL according to the following criteria:

Inclusion Criteria

- 18 years or older
- Histologically confirmed CD20+ FL grades 1 to 3a
- At least 1 measurable tumor mass
- Ann Arbor stage III or IV
- ECOG performance status 0 to 2
- Adequate bone marrow, hepatic, and renal function reserve:
    - Haemoglobin level of ≥8 g/dL,
    - ANC of ≥1500/mm^3, and
    - Platelet count of ≥75000/mm^3

Exclusion Criteria

- Prior treatment for non-Hodgkin's lymphoma
- Evidence of histological transformation to high-grade or diffuse large B-cell lymphoma

A complete list of inclusion and exclusion criteria for the study is provided in Appendix 4.

5.1.3.2 Randomization and Treatment

A total of 140 male and female patients with advanced FL were enrolled in Study CT-P10 3.3, 121 of which were included in the Part 1 PK Subset. Patients were randomized in a 1:1 ratio to receive either CT-P10 or Rituxan® (375 mg/m^2 every 3 weeks) in combination with CVP.

Randomization was stratified by country, gender, and Follicular Lymphoma International Prognostic Index (FLIPI) score (0 to 2 versus 3 to 5).

In the induction period, CT-P10 or Rituxan® at a dose of 375 mg/m^2 were co-administered with cyclophosphamide (750 mg/m^2 IV, Day 1 of each cycle), vincristine (1.4 mg/m^2 [up to a maximum of 2 mg] IV, Day 1 of each cycle), and prednisone (40 mg/m^2 oral, Day 1 to 5 of each cycle) every 3 weeks up to 8 cycles. In the maintenance period, CT-P10 or Rituxan® was administered alone every 2 months for up to 12 cycles (up to 2 years) in patients who had a response (CR, CRu or PR) at the EOT of the induction period until disease progression.

Premedication consisting of an antipyretic (e.g., paracetamol), an antihistamine (e.g., H1 antihistamine), and a glucocorticoid (prednisone on Day 1) was administered 30 minutes before each infusion of CT-P10 or Rituxan®.

5.1.3.3 Statistical Analysis

Primary Endpoint and Margin Determination

In the trial for advanced FL, ORR (CR + CRu + PR) over 8 cycles of the induction period according to the 1999 International Working Group (IWG) criteria (Cheson *et al*., 1999) has been selected as the primary endpoint in Study CT-P10 3.3.

As agreed with the EMA, Study CT-P10 3.3 was not intended initially to formally assess efficacy equivalence or non-inferiority from a primary statistical hypothesis perspective. Instead, a different approach was applied using a point estimate difference of -7% for the margin accounting for study variation in terms of ORR difference obtained from historical data between Marcus *et al*. (2005) and Federico *et al*. (2013). These studies were used to inform the eligibility criteria for Study CT-P10 3.3.

In a post-hoc fashion, the non-inferiority margin was estimated, following the FDA's guidance document *Non-inferiority clinical trials* (2010), as -7.25% preserving 50% of the lower bound of 95% CI of ORR difference between rituximab-CVP (R-CVP) treatment group (Experimental) and CVP treatment group (Control) (Figure 38), which indicates that the -7% margin preserves 52% effectiveness of Rituxan® from Marcus *et al*. (2005), the only head-to-head study to comparing R-CVP and CVP.

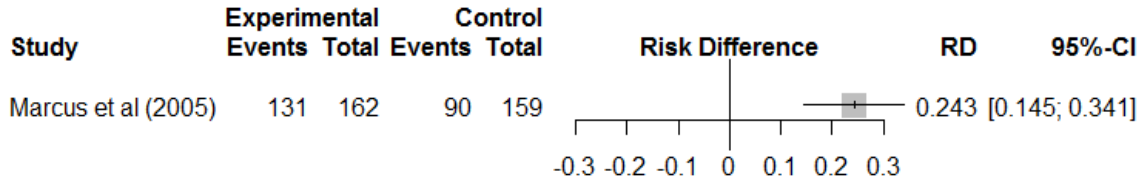


Figure 38: 95% CI of Difference in Overall Response Rate from Marcus et al. (2005)

Meta-analyses of relevant historical data, in which R-CVP group was investigated, was also conducted in a different way to justify the appropriateness of the -7% non-inferiority margin.

Preserving 50% of the difference between the lower bound of 95% CI from meta-analysis of R-CVP (0.811; Figure 39) and the upper bound of 95% CI of ORR of CVP group from Marcus *et al*. (2005), (0.644; Figure 40), the derived non-inferiority margin is -8.35%.

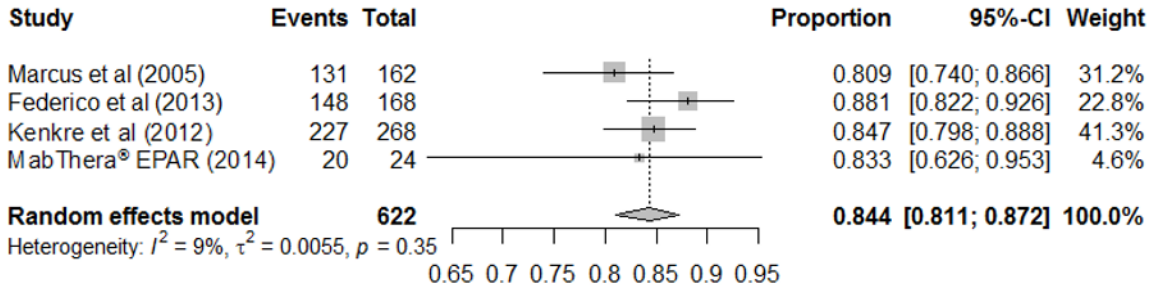


Figure 39: 95% CI of Overall Response Rate from Meta-analysis (R-CVP)

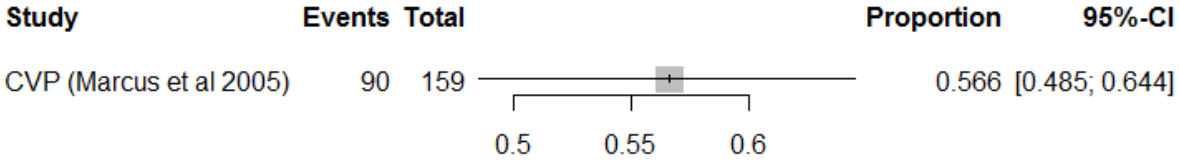


Figure 40: 95% CI of Overall Response Rate from Marcus et al. (2005) (CVP)

Taking into account the meta-analyses of historical data, the non-inferiority margin of -7% is scientifically justified.

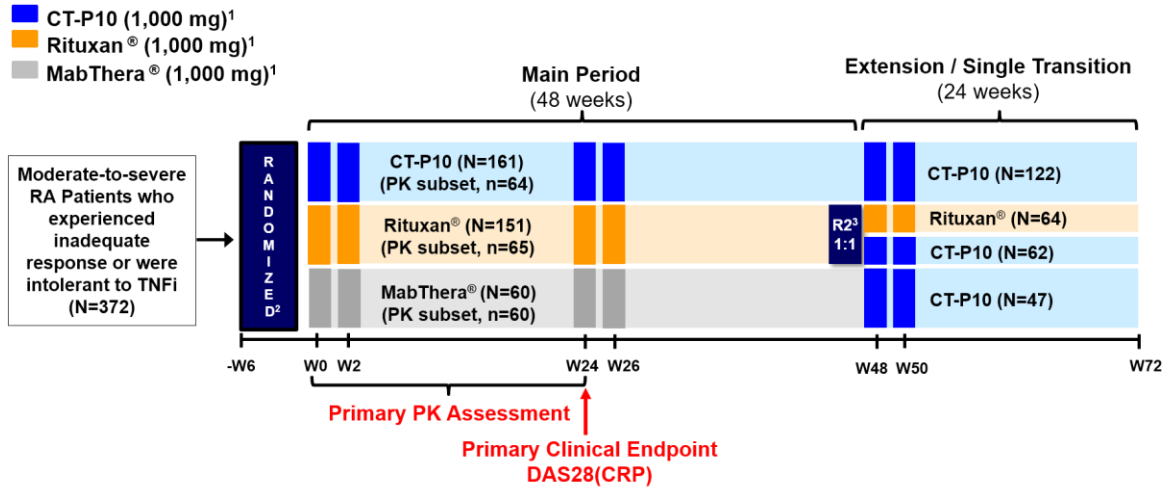
Sample Size

For the primary efficacy endpoint of Study CT-P10 3.3 (Part 2, Full Set), approximately 134 patients were required to receive CT-P10 (67 patients) or Rituxan® (67 patients) to obtain 116 evaluable patients (58 patients per treatment group), assuming a 13% dropout rate. This number of patients would allow evaluation of non-inferiority using Monte-Carlo simulation at a pre-defined margin of -7% based on the difference of point estimates of response rate in an exploratory fashion, with an 80% empirical power.

5.1.4 Study CT-P10 3.2 in Patients with Rheumatoid Arthritis

Study CT-P10 3.2 was a phase 3, randomized, active-controlled, double-blind study designed to compare CT-P10, Rituxan® and MabThera® with respect to PK, efficacy, immunogenicity and safety in patients with moderate-to-severe RA patients who experienced inadequate response or were intolerant to TNFi. The study enrolled 372 patients. The first 189 patients were included in the Part 1 PK Subset and randomized in a 1:1:1 ratio to CT-P10, Rituxan® or MabThera®. An additional 183 patients were enrolled for Part 2 Full Set for efficacy assessment and randomly assigned in a 1:1 ratio to either CT-P10 or Rituxan®. MTX was administered as background therapy in all treatment groups.

The schematic outline of the study is illustrated in Figure 41. As clinical similarity between CT-P10 and Rituxan is primarily supported by the studies in FL patients, only PK similarity and immunogenicity results from Study 3.2 are discussed.



[1] Co-administered with methotrexate and folic acid. Premedication (methylprednisolone, antipyretic, antihistamine).
[2] Stratified by prior TNFi status, RF/anti-CCP status, and country.
[3] Re-randomization.
Abbreviations: CRP, C-Reactive Protein; DAS28, Disease Activity Score using 28 Joint Counts; PK, Pharmacokinetics; RA, Rheumatoid arthritis; TNFi, Tumor necrosis factor inhibitors; W, Week
Note: Two 1,000 mg intravenous infusions of CT-P10, Rituxan® or MabThera® separated with 2 weeks were administered every 24 weeks.

Figure 41: Design of the Study CT-P10 3.2

PK similarity between CT-P10, Rituxan®, and MabThera® was demonstrated by evaluating $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} over the first 24 weeks as the primary endpoints following two 1,000 mg intravenous infusions of study drug administered 2 weeks apart. In the PK Subset, blood samples were collected for PK analysis on Weeks 0 (Days 0 and 1), 1 (Day 7), 2 (Days 14 and 15), 3 (Day 21), 4 (Day 28), 8 (Day 56), 12 (Day 84), 16 (Day 112) and 24 (Day 168). Samples were collected within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of study drug infusion, and 1 hour (±15 minutes) after the end of study drug infusion on the day of each study drug infusion.

The comparative evaluation of safety and immunogenicity was assessed as other endpoints.

5.1.4.1 Key Inclusion/Exclusion Criteria

Study CT-P10 3.2 included patients with active RA according to the following main criteria:

Inclusion Criteria

- Between 18 and 75 years old, inclusive
- A diagnosis of RA according to the revised 1987 ACR classification criteria
- Active disease as defined by the presence of

  - ≥6 swollen joints (of 66 assessed),
  - ≥6 tender joints (of 68 assessed), and
  - serum CRP ≥1.5 mg/dL or an ESR ≥28 mm/hour
- An inadequate response to previous or current treatment with tumor necrosis factor inhibitors (TNFi) agents
- Stable doses of background methotrexate (MTX) dosing
- Adequate bone marrow, hepatic, and renal function reserve

Exclusion Criteria

- Prior treatment with rituximab or more than 2 biologic agents

5.1.4.2 Randomization and Treatment

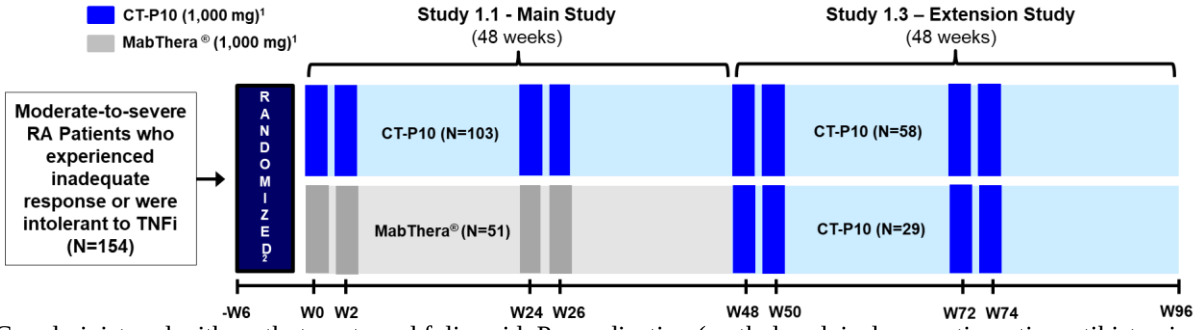
In line with the dosage and administration section of the Rituxan® USPI (2018), premedication with methylprednisolone, antipyretic and antihistamine was provided.

Randomization was stratified by country, prior TNFi treatment status (inadequate response versus intolerant) and RF or anti-CCP status (both positive vs. both negative vs. either RF or anti-CCP negative). Study treatment consisted of up to 2 courses in the main period and a third course following re-randomization in the extension period. Each course included 2 infusions of 1,000 mg rituximab, administered 2 weeks apart. For the third treatment course, patients who previously received CT-P10 remained on CT-P10; patients who previously received Rituxan® were re-randomized to receive either Rituxan® or CT-P10; and patients who previously received MabThera® were transitioned to CT-P10. The extension period generated efficacy, safety and immunogenicity data following a single-transition from the reference product to the biosimilar product. The treatment period including the extension period was 72 weeks (3 courses of treatment).

5.1.5 Study CT-P10 1.1 and CT-P10 1.3 in Patients with Rheumatoid Arthritis

Studies CT-P10 1.1 and 1.3 provide supportive PK and immunogenicity data to establish the similarity of CT-P10 to Rituxan® as they were conducted against EU-approved MabThera®.

The schematic outline of these studies is shown in Figure 42.



[1] Co-administered with methotrexate and folic acid. Premedication (methylprednisolone, antipyretic, antihistamine).
[2] Stratified by region (European vs. non-European) and prior anti-TNF-α blocker status (failure vs. intolerant case).
Abbreviations: RA, Rheumatoid arthritis; TNFi, Tumor necrosis factor inhibitors; W, Week
Note: Two 1,000 mg intravenous infusions of CT-P10, Rituxan® or MabThera® separated with 2 weeks were administered every 24 weeks. For background therapy, MTX was administered at a dose of 7.5-25 mg orally or parenterally every week with folic acid at a dose of at least 5 mg/week. Premedication consisted of 100 mg methylprednisolone administered intravenous 30 minutes before each infusion of study drug, antipyretic (acetaminophen or paracetamol, usually 500-1,000 mg) and an antihistamine (chlorpheniramine 2-4 mg, or equivalent) 30-60 minutes before study drug infusion.

Figure 42: Design of Studies CT-P10 1.1 and CT-P10 1.3

Key inclusion and exclusion criteria were consistent with those used in Study CT-P10 3.2.

5.2 Clinical Pharmacology Results

5.2.1 Pharmacokinetics

For ethical reasons, no clinical pharmacology studies in healthy subjects were deemed appropriate. The PK of intravenously administered rituximab has been previously characterized in patients with NHL and RA (Rituxan® USPI, 2018; MabThera® SmPC, 2018; Genentech, Inc., 2017).

5.2.1.1 PK Similarity Study in Patients with Advanced Follicular Lymphoma (Study CT-P10 3.3)

As CVP chemotherapy regimen has no reported impact on the PK of rituximab, the choice of the study population and background regimen was considered appropriate for evaluation of PK similarity in an oncology indication (Plosker & Figgit, 2003; Genentech, Inc., 2017).

In Study CT-P10 3.3, AUC_{tau} and $C_{max,ss}$ at Cycle 4 (9-12 weeks) were the co-primary PK endpoints to demonstrate that CT-P10 is similar to Rituxan® in terms of PK in advanced FL patients. Based on the PK profile of rituximab in published NHL studies and as confirmed by observations in Study CT-P10 3.3, steady state is reached at the 4th cycle of treatment (Jäger *et al.*, 2012; Blasco *et al.*, 2009; Berinstein *et al.*, 1998); thus it was appropriate to assess AUC_{tau} and $C_{max,ss}$ at Cycle 4. A range of secondary PK endpoints up to Cycle 8 were assessed to provide additional information on the PK profiles of CT-P10 and Rituxan®, as detailed in Table 12.

Table 12: PK Parameters Evaluated in Study CT-P10 3.3

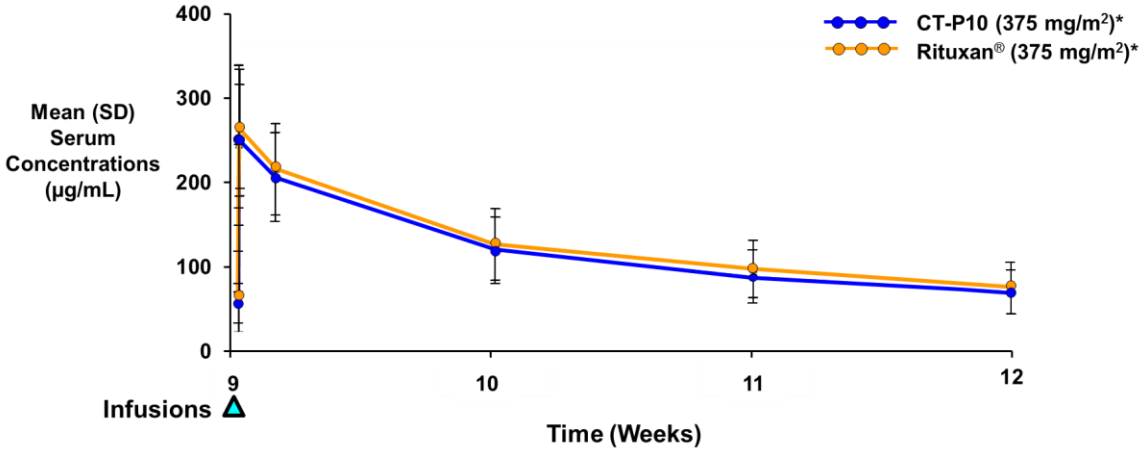
Clinical Assessment		Endpoints
PK	Primary	AUC_{tau}; $C_{max,ss}$ at Cycle 4 (9 - 12 weeks)
	Secondary	C_{max} at each dose; C_{trough} at each dose; $C_{trough,ss}$; $C_{av,ss}$; V_{ss}; CL_{ss}; $T_{1/2}$; $T_{max,ss}$; MRT; PTF_{ss}; λ_z at Cycle 4 (9 – 12 weeks)

The 90% CIs of the geometric LS mean ratios (CT-P10 to Rituxan® group) for AUC_{tau} and $C_{max,ss}$ were entirely contained in the PK similarity range of 80% to 125%, which indicates that rituximab exposures for CT-P10 are similar to those for Rituxan®. Results from the primary PK analyses are presented in Table 13.

Table 13: Primary PK Analyses (AUC_{tau} and $C_{max,ss}$) by ANCOVA for CT-P10 and Rituxan® in Study CT-P10 3.3: PK Subset (n=121)

Treatment and Comparison	AUC_{tau} (h•µg/mL)	$C_{max,ss}$ (µg/mL)
Geometric LS Mean [Number of Patients]		
CT-P10	30651 [55]	226 [55]
Rituxan®	32160 [58]	223 [58]
Ratio of Geometric LS Means (90% CI) (%)		
CT-P10 vs. Rituxan®	95.31 (81.01 - 112.13)	101.38 (93.49 - 109.94)

The linear concentration-time profiles during Cycle 4 (9 - 12 weeks) for CT-P10 and Rituxan® are nearly identical, as illustrated in Figure 43.



* Co-administered with Cyclophosphamide, Vincristine, and Prednisone (CVP)

Figure 43: Mean (±SD) Serum Concentration of CT-P10 and Rituxan® During Cycle 4 (9 - 12 Weeks) at Steady State in Study CT-P10 3.3: PK Subset (n=121)

5.2.1.2 PK Study in Patients with Low Tumor Burden Follicular Lymphoma (LTBFL) (Study CT-P10 3.4)

In the Study CT-P10 3.4, C_{max} and C_{trough} at each dose over 7 months were assessed as the secondary PK endpoints using descriptive statistics to demonstrate that CT-P10 is similar to Rituxan® in terms of PK in LTBFL patients, as presented in Table 14. No formal PK similarity criteria were employed in Study CT-P10 3.4 because PK similarity had already been established using the FDA recommended criteria in Study CT-P10 3.3 in advanced FL and in Study CT-P10 3.2 in RA. Therefore, the assessment of PK was conducted descriptively.

Table 14: PK Endpoints in Study CT-P10 3.4

Clinical Assessment		Endpoints
PK	Secondary	C_{max}, C_{trough} at each dose

The mean C_{max} and C_{trough} of CT-P10 and Rituxan® in Study CT-P10 3.4 were closely overlapped at each time point. The linear concentration-time profiles are nearly identical, as illustrated in Figure 44.

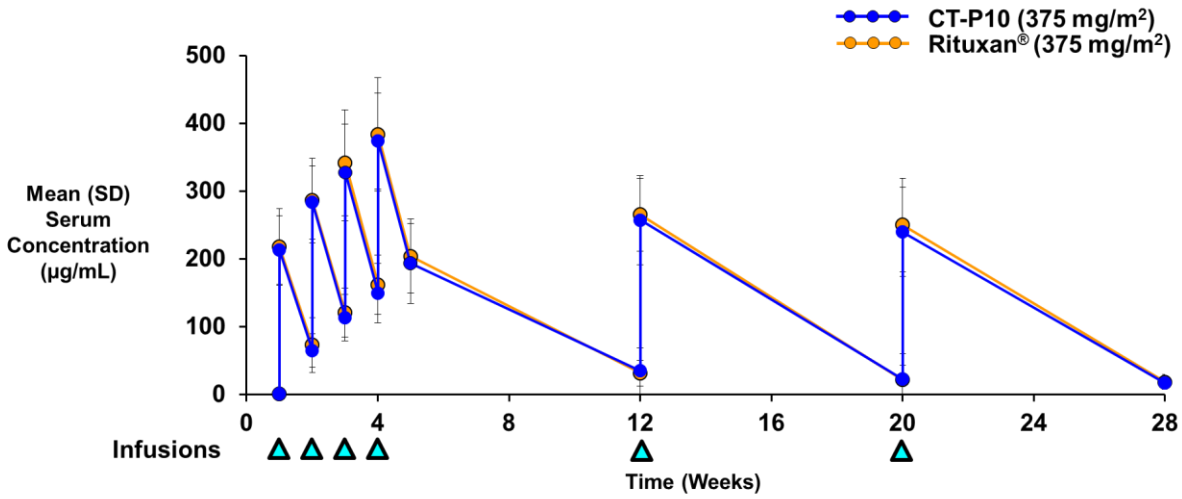


Figure 44: Mean (±SD) Serum Concentration of CT-P10 and Rituxan® in Linear Scale in Study CT-P10 3.4: PK Population (n=256)

5.2.1.3 PK Similarity Study in Patients with Rheumatoid Arthritis (Study CT-P10 3.2)

In Study CT-P10 3.2, a range of PK endpoints were assessed to compare the PK profile of CT-P10 to both Rituxan® and MabThera®, as detailed in Table 15.

Table 15: PK Parameters Evaluated in Study CT-P10 3.2

Clinical Assessment		Endpoint	
		Part 1 (PK Subset)	Part 2 (Full Set)
PK	Primary	$AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} over the first 24 weeks	N/A
	Secondary	$AUC_{0\text{-day14}}$, V_d, CL, $T_{1/2}$, $C_{max,1}$[1], T_{max}, C_{min} and C_{trough} over the first 24 weeks	C_{max}, T_{max}, C_{min}, C_{trough} and C_{max1}[1], over 48 weeks

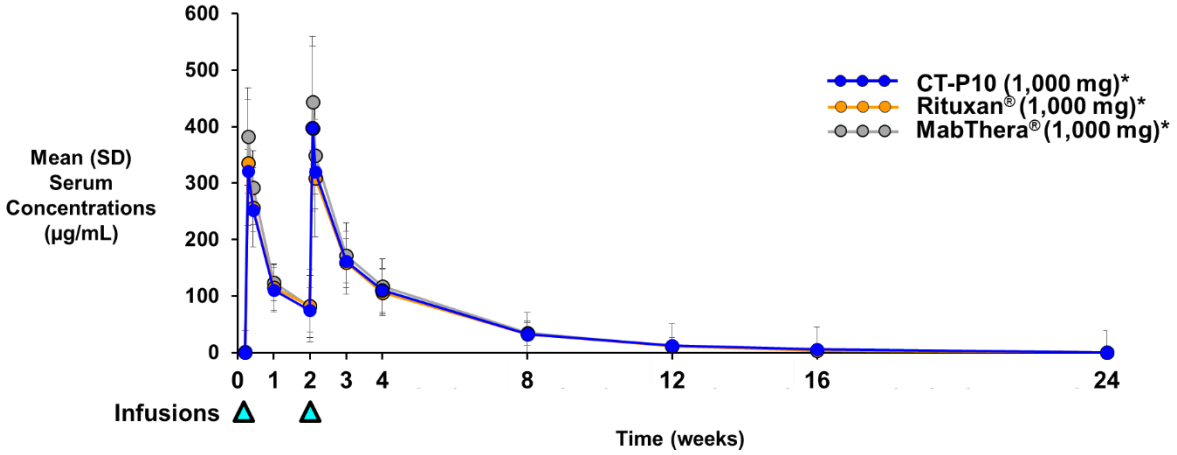
[1] $C_{max,\,1}$: Observed maximum concentration following the 1st infusion of the 1st treatment of each course

For the primary analysis in the PK population, the 90% CIs of the ratios of geometric LS means for all primary PK endpoints ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}) were entirely contained in the PK similarity margin of 80% to 125%. This demonstrates that rituximab exposure was similar in all 3 comparisons between 1) CT-P10 and Rituxan®, 2) CT-P10 and MabThera® and 3) Rituxan® and MabThera®. PK similarity is also supported by the additional key PK endpoint assessment ($AUC_{0\text{-day14}}$) requested by FDA; the 90% CIs of the ratios of geometric LS means for $AUC_{0\text{-day14}}$ were also contained within the PK similarity margin of 80-125% in the 3-way comparisons. The results of these PK analyses are presented in Table 16.

Table 16: PK Analyses ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, $AUC_{0\text{-day14}}$) by ANCOVA for CT-P10, Rituxan® and MabThera® in Study CT-P10 3.2: PK Population (n=184)

Treatment and Comparison	$AUC_{0\text{-last}}$ (h•µg/mL)	$AUC_{0\text{-inf}}$ (h•µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-day14}}$ (h•µg/mL)
Geometric LS Mean [Number of Patients]				
CT-P10	163216 [62]	163055 [59]	378 [62]	43356 [62]
Rituxan®	160266 [63]	164855 [62]	373 [63]	44939 [63]
MabThera®	173485 [59]	181353 [56]	425 [59]	48985 [59]
Ratio of Geometric LS Means (90% CI) (%)				
CT-P10 vs. Rituxan®	101.84 (91.77 - 113.01)	98.91 (89.77 - 108.97)	101.39 (94.00 - 109.35)	96.48 (89.50 - 104.00)
CT-P10 vs. MabThera®	94.08 (84.63 - 104.58)	89.91 (81.40 - 99.31)	88.99 (82.40 - 96.10)	88.51 (82.00 - 95.53)
MabThera® vs. Rituxan®	108.25 (97.32 - 120.40)	110.01 (99.64 - 121.45)	113.93 (105.45 - 123.09)	109.00 (100.95 - 117.70)

The linear concentration-time profiles for CT-P10, Rituxan® and MabThera® are nearly identical, as illustrated in Figure 45.



* Co-administered with methotrexate and folic acid

Figure 45: Mean (±SD) Serum Concentration of CT-P10, Rituxan® and MabThera® in Study CT-P10 3.2: PK Population (n=184)

Similar PK findings were obtained from Study CT-P10 1.1.

5.2.1.4 Conclusions

In summary, PK similarity between CT-P10 and Rituxan® is supported by PK data from patients with advanced FL, LTBFL, and RA. In patients with advanced FL, PK similarity was demonstrated between CT-P10 and Rituxan® by relevant steady state PK endpoints during the 4th cycle of rituximab treatment on background of CVP. These results show that CT-P10 and the reference product (Rituxan®) provide similar exposure following repeated cyclical dosing, supporting PK similarity in NHL. PK similarity in NHL indications is also supported by findings from Study CT-P10 3.4 in LTBFL patients receiving rituximab monotherapy. In addition, PK similarity of CT-P10 versus Rituxan®/MabThera® was confirmed by the findings from Study CT-P10 3.2 and CT-P10 1.1 in RA patients.

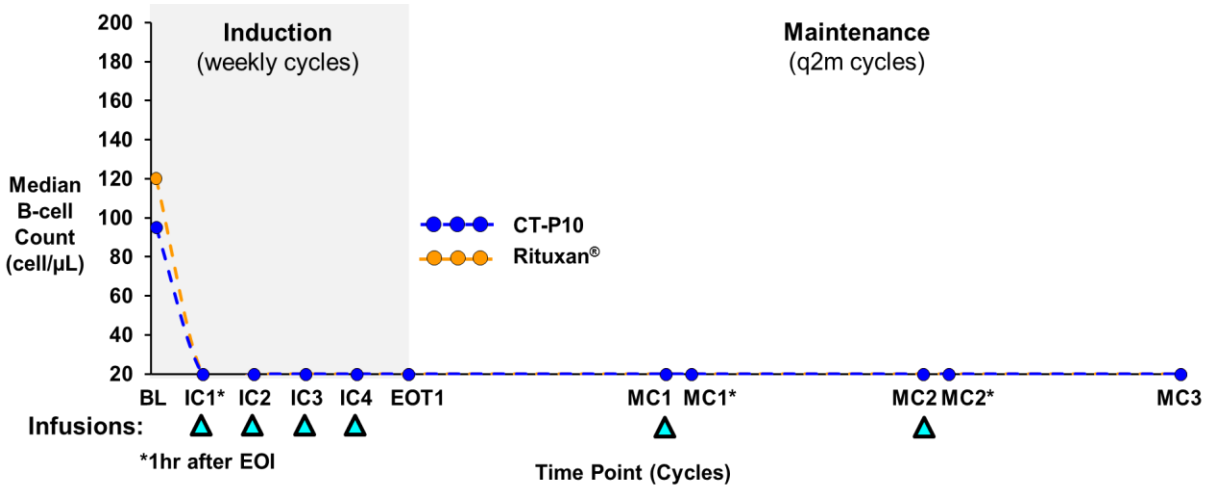
In conclusion, the PK data from CT-P10 clinical studies support clinical similarity between CT-P10 and Rituxan® for the Proposed Indications (Section 1.1).

5.2.2 Pharmacodynamics

In the CT-P10 clinical development program, the longitudinal dynamics of B-cell depletion was evaluated in Studies CT-P10 3.4 and CT-P10 3.3.

5.2.2.1 PD Similarity in Patients with Low Tumor Burden Follicular Lymphoma (Study CT-P10 3.4)

In Study CT-P10 3.4, median peripheral B-cell counts decreased to below the lower limit of quantification (LLoQ; 20 cells/µL) after the first infusion and remained below the LLoQ at each subsequent cycle over 7 months, as shown in Figure 46. These data indicate that the extent of B-cell depletion in patients with LTBFL was similar between CT-P10 and Rituxan®.

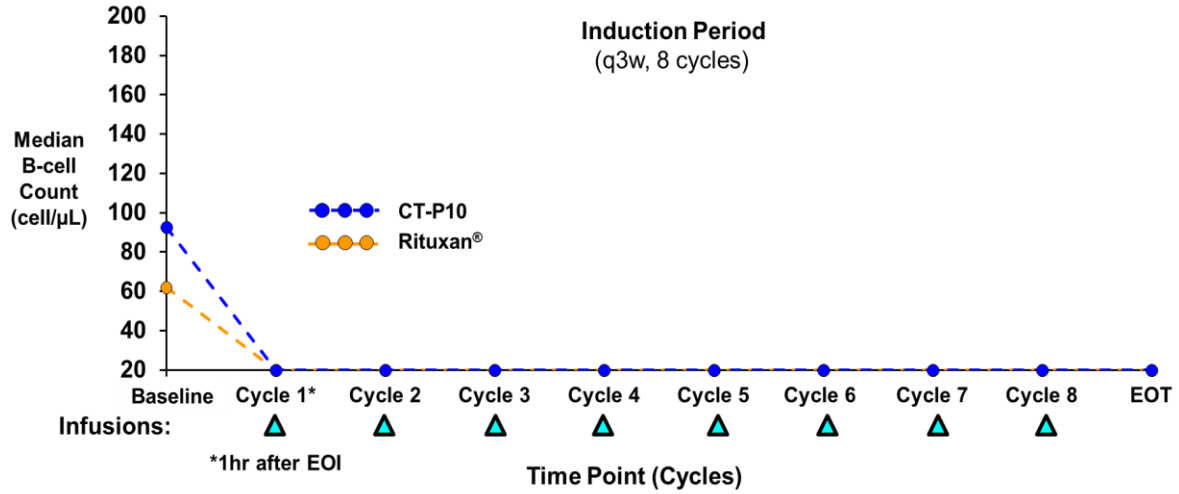


Abbreviations: BL, Baseline; EOI, End of infusion; EOT, End of treatment; IC, Induction Cycle; MC, Maintenance Cycle; q2m, Every 2 months
Note: Any values below the lower limit of quantification (LLoQ) were set as LLoQ which was 20 cells/µL.

Figure 46: Median B-cell Counts in Patients Receiving CT-P10 or Rituxan® in Study CT-P10 3.4: PD Population (n=256)

5.2.2.2 PD Similarity in Patients with Advanced Follicular Lymphoma (Study CT-P10 3.3)

Median peripheral B-cell counts decreased to below the LLoQ (20 cells/µL) after the first infusion and remained below the LLoQ at each subsequent cycle (prior to dosing) over 8 cycles (24 weeks; shown in Figure 47). These data indicate that the extent of B-cell depletion in patients with advanced FL was similar between CT-P10 and Rituxan®. The pattern of B-cell depletion in Study CT-P10 3.3 was consistent with that reported in the literature in NHL studies with Rituxan®/MabThera® (Davies *et al.*, 2017; Genentech, Inc., 2017).



Abbreviations: EOI, End of infusion; EOT, End of treatment; q3w, Every 3 weeks
Note: Any values below the lower limit of quantification (LLoQ) were set as LLoQ which was 20 cells/µL.

Figure 47: Median B-cell Counts in Patients Receiving CT-P10 or Rituxan® during Induction Period in Study CT-P10 3.3: PD Population (n=140)

5.2.2.3 Conclusions

In summary, B-cell depletion was similar between CT-P10 and Rituxan® groups in patients with FL and consistent with that reported with Rituxan®.

In conclusion, the PD data from CT-P10 FL clinical studies support clinical similarity between CT-P10 and Rituxan® for the Proposed Indications (Section 1.1).

5.3 Clinical Efficacy Results

5.3.1 Study CT-P10 3.4 in Patients with Low Tumor Burden Follicular Lymphoma (LTBFL)

5.3.1.1 Patient Disposition

A total of 258 patients were randomized in the study, making up the ITT population: 130 patients in the CT-P10 group and 128 patients in the Rituxan® group. All randomized patients in the ITT population received at least 1 dose of CT-P10 and Rituxan®, respectively. Patient disposition is provided in Figure 48.

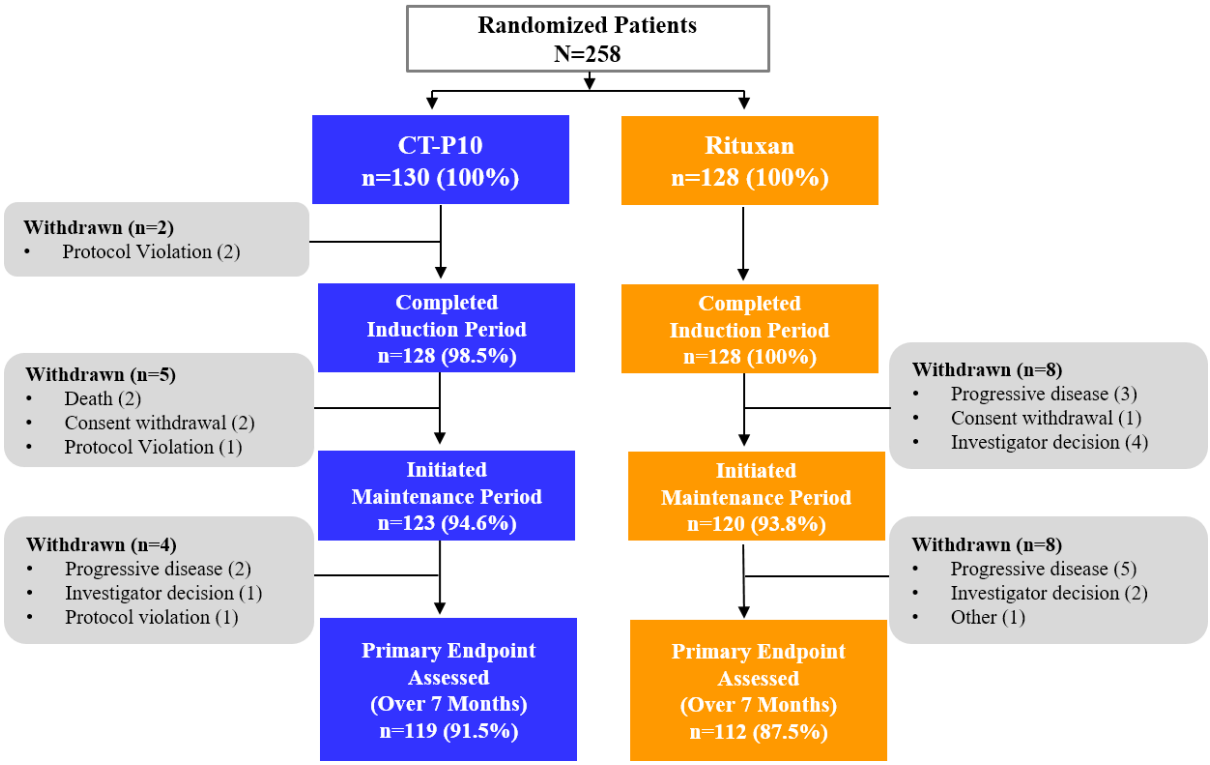


Figure 48: Patient Disposition in Study CT-P10 3.4

All randomized patients in the CT-P10 and Rituxan® groups initiated study treatment and a total of 231 patients (119/130 [91.5%] and 112/128 [87.5%] patients in the CT-P10 and Rituxan® groups, respectively) completed study treatment over 7 months (induction period [weekly, 4 cycles]

and 2 cycles of maintenance period [2-monthly]) while 27 patients (11/130 [8.5%] and 16/128 [12.5%] patients in the CT-P10 and Rituxan® groups, respectively) discontinued the study over 7 months. The most frequently reported reason for discontinuation over 7 months was protocol violation (4/130 [3.1%] patients) in the CT-P10 group and disease progression (8/128 [6.3%] patients) in the Rituxan® group.

Overall, the number of patients who received the study drug was similar in the CT-P10 and Rituxan® groups, as was the incidence of any reasons for discontinuation study drug and discontinuation of the study itself. In addition, the relative dose intensity of rituximab was similar between the CT-P10 and Rituxan® groups.

5.3.1.2 Patient Demographics and Disease Characteristics

In Study CT-P10 3.4, overall demographic and disease characteristics were balanced between the 2 treatment groups, as shown in Table 17. The study was conducted in North America (with sites in US), Europe, Asia Pacific and Latin America. The demographic and baseline characteristics of subjects enrolled in this study were consistent with those found in the historical Ardeshna *et al.* (2014) study.

Table 17: Demographic and Disease Characteristics in Study CT-P10 3.4: ITT Population

Baseline	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Age (years)		
Median (Minimum, maximum)	58.0 (19, 82)	59.0 (35, 88)
Gender		
Male	66 (50.8)	57 (44.5)
Female	64 (49.2)	71 (55.5)
Race		
White or Caucasian	77 (59.2)	75 (58.6)
Asian	47 (36.2)	49 (38.3)
American Indian or Alaska Native	3 (2.3)	3 (2.3)
Other	3 (2.3)	1 (0.8)
Ethnicity		
Not Hispanic or Latino	110 (84.6)	116 (90.6)
Hispanic or Latino	12 (9.2)	10 (7.8)
Unknown	8 (6.2)	2 (1.6)
Region		
Europe	67 (51.5)	63 (49.2)
Asia Pacific	50 (38.5)	51 (39.8)
North America	4 (3.1)	4 (3.1)

Baseline	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Other	9 (6.9)	10 (7.8)
Height (cm)		
Mean ± SD	167.4 ± 9.29	164.7 ± 10.37
Weight (kg)		
Mean ± SD	73.33 ± 17.289	68.98 ± 17.022
BSA (m^2)		
Mean ± SD	1.838 ± 0.2466	1.767 ± 0.2550
ECOG Performance Status at Screening		
Grade 0	109 (83.8)	108 (84.4)
Grade 1	21 (16.2)	20 (15.6)
Ann Arbor Staging at Screening		
Stage I	1 (0.8)[#]	0
Stage II	31 (23.8)	30 (23.4)
Stage III	47 (36.2)	53 (41.4)
Stage IV	51 (39.2)	45 (35.2)
FLIPI Score at Screening		
0	18 (13.8)	17 (13.3)
1	40 (30.8)	35 (27.3)
2	46 (35.4)	49 (38.3)
3	24 (18.5)	24 (18.8)
4	2 (1.5)	3 (2.3)
5	0	0
GELF Criteria		
No-B symptoms	130 (100)	128 (100)
Normal Serum LDH	128 (98.5)	126 (98.4)
No target nodal/extranodal mass >7cm	130 (100)	128 (100)
<3 nodal sites, each with a diameter ≥3cm	127 (97.7)	127 (99.2)
No serous effusions	130 (100)	128 (100)
No splenomegaly (defined as ≤16cm)	128 (98.5)	128 (100)
No cytopenia[*]	130 (100)	128 (100)
FL Grade at Screening (central)		
Grade 1	26 (20.0)	32 (25.0)
Grade 2	92 (70.8)	84 (65.6)
Grade 3a	12 (9.2)	12 (9.4)

Baseline	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Number of extra-nodal sites (central)		
0-1	128 (98.5)	123 (96.1)
≥ 2	2 (1.5)	5 (3.9)
Bone Marrow Assessment at Screening		
Negative	82 (63.1)	87 (68.0)
Positive	46 (35.4)	41 (32.0)
Missing	2 (1.5)	0
Beta-2 Microglobulin at Screening		
Beta-2 microglobulin <3.0	105 (80.8)	104 (81.3)
Beta-2 microglobulin ≥3.0	18 (13.8)	21 (16.4)
Missing	7 (5.3)	3 (2.3)

[#] This patient was enrolled with stage II disease but it was corrected to stage I following investigator's reconfirmation. The patient was included in the ITT population and was analyzed in the category of "Lower than or equals to II" for the corresponding analysis.
[*] Platelets < $100x10^9$/L, hemoglobin <10 g/dL, or ANC <$1.5x10^9$/L.

5.3.1.3 Efficacy Results – Primary Endpoint

The primary efficacy endpoint for Study CT-P10 3.4, ORR over 7 months, is presented in Table 18. ORR was calculated as best overall response over 7 months and assessed by central review.

The proportion of patients achieving an ORR over 7 months in the ITT population was 83.1% (108/130) in the CT-P10 group compared to 81.3% (104/128) in the Rituxan® group. The difference in ORR between the treatment groups was 1.8%.

In an exact binomial test, the 90% exact CI for the treatment difference was entirely within the equivalence margin of ±17% agreed with FDA, thus meeting the pre-specified criteria for therapeutic equivalence between the treatment groups (90% exact CI [-6.43, 10.20] for the ITT population; [-4.56, 11.56] for the PP population).

The 7-month ORR results observed in Study CT-P10 3.4 were consistent with those from Ardeshna *et al*. (2014) (88% in Ardeshna *et al*. [2014]; 86.8% and 83.3% in the CT-P10 and Rituxan® groups, respectively, in the PP population from Study CT-P10 3.4).

Table 18: Proportion of Patients Achieving Overall Response over 7 Months in Study CT-P10 3.4: ITT and PP Populations - Central Review

n/N (%)	CT-P10	Rituxan®	Treatment Difference Estimate [90% Exact CI]
ITT Population			
ORR (CR + CRu + PR)	108/130 (83.1)	104/128 (81.3)	1.8% [-6.43, 10.20]
CR	36/130 (27.7)	43/128 (33.6)	-
CRu	6/130 (4.6)	2/128 (1.6)	-
PR	66/130 (50.8)	59/128 (46.1)	-
Stable disease	17/130 (13.1)	18/128 (14.1)	-
Progressive disease/Relapsed disease	0	4/128 (3.1)	-
Unable to assess	0	1/128 (0.8)	-
Missing	5/130 (3.8)	1/128 (0.8)	
PP Population			
ORR (CR+CRu+PR)	99/114 (86.8)	100/120 (83.3)	3.5% [-4.56, 11.56]
CR	35/114 (30.7)	41/120 (34.2)	-
CRu	6/114 (5.3)	2/120 (1.7)	-
PR	58/114 (50.9)	57/120 (47.5)	-
Stable disease	15/114 (13.2)	15/120 (12.5)	-
Relapsed disease/Progressive disease	0	4/120 (3.3)	-
Unable to assess	0	1/120 (0.8)	-

5.3.1.4 Overall Response Rate (Sensitivity Analysis: Logistic Regression)

The sensitivity analysis (logistic regression method with treatment as fixed effect and region, Ann Arbor stage, and age as covariates) of ORR over 7 months indicated similar results to the main analyses for both the ITT and PP populations (Table 19). The 90% CI of the treatment difference estimate was entirely within the ±17% equivalence margin (90% CI [-6.20, 9.36] for the ITT population; [-4.11, 10.80] for the PP population).

Table 19: Logistic Regression for ORR (CR+CRu+PR) over 7 Months in Study CT-P10 3.4: ITT and PP Populations - Central Review

Population Treatment	Overall Response Rate n/N (%)	Estimate (%)[1]	Treatment Difference Estimate (%)	90% CI of Treatment Difference
ITT Population				
CT-P10	108/130 (83.1)	83.7	1.6	(-6.20, 9.36)
Rituxan®	104/128 (81.3)	82.2		
PP Population				
CT-P10	99/114 (86.8)	88.2	3.3	(-4.11, 10.80)
Rituxan®	100/120 (83.3)	84.9		

[1] The estimate of the proportions was calculated using a logistic regression model, with treatment as a fixed effect and region (Asia Pacific vs. Europe vs. North America and other), Ann Arbor stage (lower than or equal to II vs. III vs. IV), and age (≥60 vs. <60 years) as covariates.

5.3.1.5 Missing Data: Tipping Point Analysis

A tipping point analysis was conducted for ORR, under "missing not at random" scenarios. Patients with no response evaluation data or "unable to assess" were imputed as "responders" in a gradual shift for each treatment group. The 90% CIs of the difference in the proportion between the 2 treatment groups were calculated using asymptotic methods and scenarios were displayed as a shift table (Table 20). The tipping point analyses showed that missing data had no discernible impact on the results of the primary efficacy endpoint. Under all possible scenarios using the assumed number of responders in each group, the 90% CIs were entirely contained within the equivalence margin of ±17%. These results support the therapeutic equivalence between the treatment groups from the primary analysis.

Table 20: Tipping Point Analysis for ORR (CR+CRu+PR) over 7 Months in Study CT-P10 3.4: ITT Population - Central Review

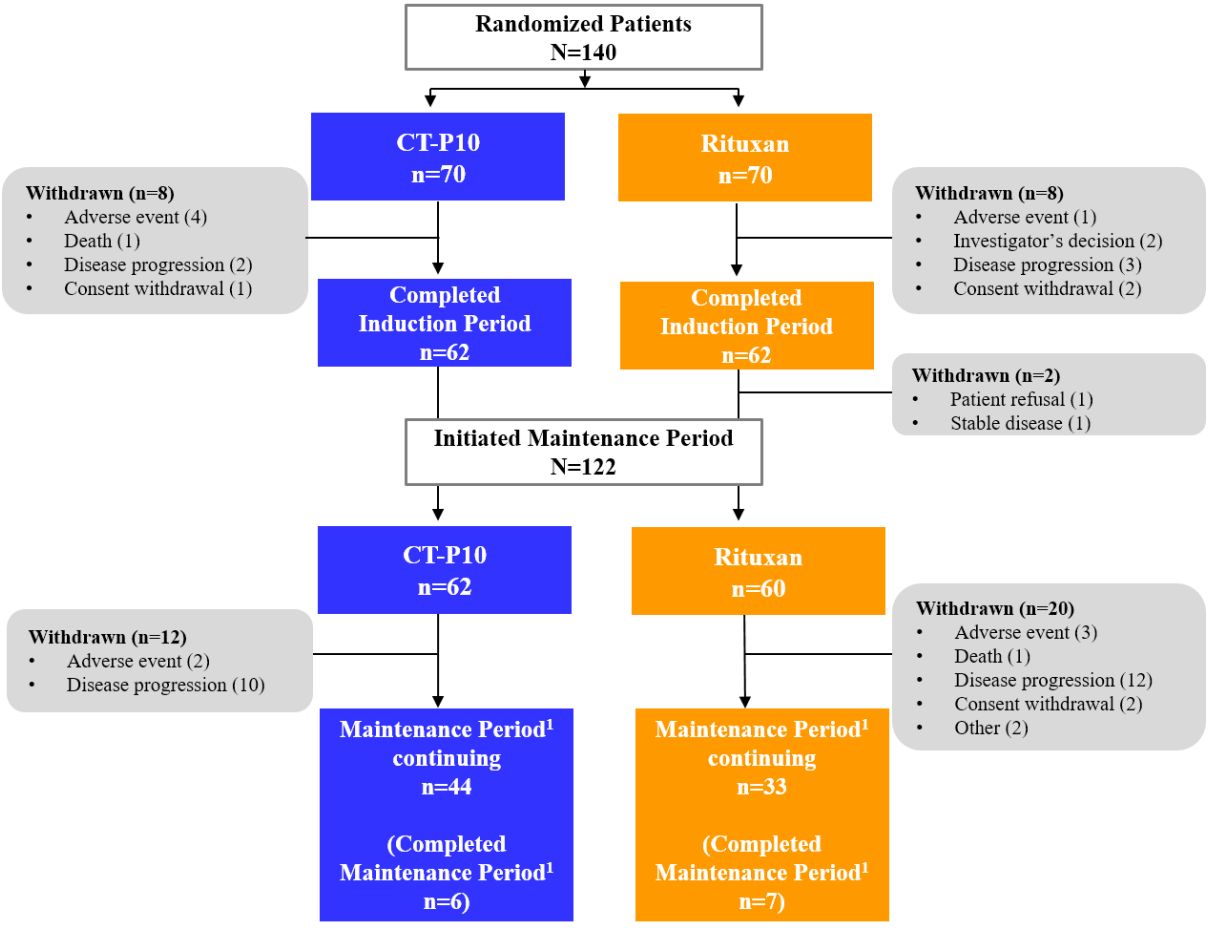
90% CI for the Treatment Difference			
Shift for CT-P10 Group[1]	**Shift for Rituxan® Group[1]**		
	0	**+1**	**+2**
0	(-6.01, 9.67)	(-6.73, 8.82)	(-7.44, 7.97)
+1	(-5.17, 10.37)	(-5.89, 9.52)	(-6.60, 8.67)
+2	(-4.33, 11.07)	(-5.05, 10.22)	(-5.76, 9.36)
+3	(-3.49, 11.76)	(-4.20, 10.91)	(-4.92, 10.06)
+4	(-2.65, 12.46)	(-3.36, 11.60)	(-4.07, 10.75)
+5	(-1.80, 13.15)	(-2.51, 12.30)	(-3.22, 11.44)

[1] Assumed number of responder for patients with no response evaluation result or 'unable to assess' in each group.

5.3.2 Study CT-P10 3.3 in Patients with Advanced Follicular Lymphoma

5.3.2.1 Patient Disposition

A total of 140 patients were randomized in the study, making up the ITT population: 70 patients in the CT-P10 group and 70 patients in the Rituxan® group. All randomized patients in the ITT population received at least 1 dose of CT-P10 and Rituxan®, respectively. Patient disposition is provided in Figure 49.



[1] Up to the cut-off date (July 31, 2017)

Figure 49: Patient Disposition in Study CT-P10 3.3

During the induction period in the ITT population, all patients received at least 1 course of study treatment in the CT-P10 and Rituxan® groups. The number of patients who completed the R+CVP induction period (62/70 [88.6%] in both groups) and entered maintenance period was similar between the CT-P10 and Rituxan® groups (62/70 [88.6%] and 60/70 [85.7%], respectively). As of the cut-off date, 50 patients (20/70 [28.6%] and 30/70 [42.9%] patients in the CT-P10 and Rituxan® groups, respectively) discontinued the treatment during the study period including induction and maintenance periods. The most frequently reported reason for discontinuation up to the cut-off date was disease progression (12/70 [17.1%] and 15/70 [21.4%] patients in the CT-P10 and Rituxan® groups, respectively). Overall, the number of patients who received the study drug

and CVP chemotherapy was comparable in the CT-P10 and Rituxan® groups, as was the incidence of and reasons for discontinuation of the study drug and chemotherapy, and discontinuation of the study itself. In addition, the relative dose intensity of rituximab and CVP were similar between the CT-P10 and Rituxan® groups.

5.3.2.2 Patient Demographics and Disease Characteristics

In Study CT-P10 3.3, the overall demographics and disease baseline characteristics were balanced between CT-P10 and Rituxan® as shown in Table 21. The study was conducted in Europe, Africa, Asia Pacific and Latin America.

Table 21: Demographic and Disease Characteristics in Study CT-P10 3.3: ITT Population

Baseline	CT-P10+CVP N=70	Rituxan®+CVP N=70
	Number (%) of Patients	
Age (years)		
Median (Minimum, maximum)	57.0 (30, 85)	58.5 (26, 84)
Gender		
Male	30 (42.9)	33 (47.1)
Female	40 (57.1)	37 (52.9)
Race		
White or Caucasian	51 (72.9)	52 (74.3)
Asian	11 (15.7)	13 (18.6)
Hispanic or Latino	6 (8.6)	3 (4.3)
Black or African American	2 (2.9)	0 (0)
Other	0 (0)	2 (2.9)
Height (cm)		
Mean ± SD	166.9 ± 9.19	164.9 ± 9.83
Weight (kg)		
Mean ± SD	73.2 ± 15.67	72.0 ± 15.32
ECOG Performance Status at Screening		
0	44 (62.9)	47 (67.1)
1	25 (35.7)	22 (31.4)
2	1 (1.4)	1 (1.4)
FLIPI score at Screening		
1	8 (11.4)	6 (8.6)
2	25 (35.7)	21 (30.0)

Baseline	CT-P10+CVP N=70	Rituxan®+CVP N=70
	Number (%) of Patients	
3	23 (32.9)	30 (42.9)
4	10 (14.3)	12 (17.1)
5	4 (5.7)	1 (1.4)
Ann Arbor Staging at Screening		
Stage III	21 (30.0)	36 (51.4)
Stage IV	49 (70.0)	34 (48.6)
FL grade at Screening		
Grade 1	21 (30.0)	20 (28.6)
Grade 2	36 (51.4)	34 (48.6)
Grade 3a	12 (17.1)	16 (22.9)
Missing[#]	1 (1.4)	0
B-Symptoms		
All absent	53 (75.7)	50 (71.4)
At least 1 present	17 (24.3)	20 (28.6)
Bulky disease (Lesion size≥7cm)		
No	59 (84.3)	55 (78.6)
Yes	11 (15.7)	14 (20.0)
Missing	0	1 (1.4)
Number of extra-nodal sites		
0-1	65 (92.9)	68 (97.1)
≥2	5 (7.1)	1 (1.4)
Missing	0	1 (1.4)
Bone marrow Involvement		
Positive	45 (64.3)	33 (47.1)
Negative	25 (35.7)	37 (52.9)

[#] One patient in the CT-P10 group, did not have source document to identify FL grade but FL was diagnosed with bone marrow specimen. This patient was excluded from the PP population due to this major protocol violation.

Overall, the demographic and baseline characteristics of subjects enrolled in this study were consistent with those found in historical study by Marcus *et al*. (2008) in patients with advanced FL treated with rituximab on background of CVP.

5.3.2.3 Efficacy Results – Primary Endpoint

The primary efficacy endpoint in Study CT-P10 3.3, ORR (CR + CRu + PR) calculated as best overall response during the induction period and assessed by central review according to 1999 IWG criteria, is presented in Table 22.

The ORR through the induction period in the ITT population was 95.7% (67/70) in the CT-P10 group compared to 90.0% (63/70) in the Rituxan® group. This was associated with a treatment difference of 5.7%, of which the lower bound of 95% CI (-3.41%) was on the positive side of the -7% non-inferiority margin based on the variability of rituximab. The non-inferiority criterion was met with the descriptive point estimate difference approach as well as the formal statistical non-inferiority test at a 2.5% significance level.

Table 22: Proportion of Patients Achieving Overall Response through Induction Period in Study CT-P10 3.3: ITT and PP Populations - Central Review

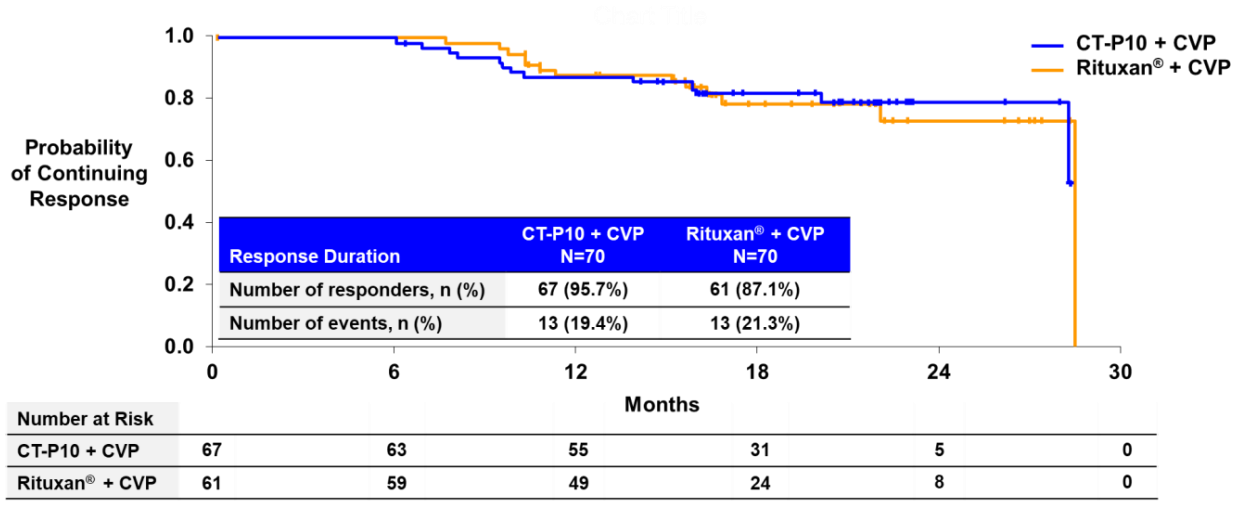
n (%)	CT-P10	Rituxan®	Difference [lower bound of 95% CI]
ITT Population			
ORR (CR+CRu+PR)	67/70 (95.7)	63/70 (90.0)	5.7% [-3.41]
CR	21/70 (30.0)	15/70 (21.4)	-
CRu	6/70 (8.6)	8/70 (11.4)	-
PR	40/70 (57.1)	40/70 (57.1)	-
Stable disease	1/70 (1.4)	2/70 (2.9)	-
Relapsed disease/Progressive disease	1/70 (1.4)	2/70 (2.9)	-
Unable to assess	0	1/70 (1.4)	-
Missing	1/70 (1.4)	2/70 (2.9)	-
PP Population			
ORR (CR+CRu+PR)	64/66 (97.0)	63/68 (92.6)	4.3% [-4.25]
CR	20/66 (30.3)	15/68 (22.1)	-
CRu	6/66 (9.1)	8/68 (11.8)	-
PR	38/66 (57.6)	40/68 (58.8)	-
Stable disease	1/66 (1.5)	2/68 (2.9)	-
Relapsed disease/Progressive disease	1/66 (1.5)	2/68 (2.9)	-
Unable to assess	0	1/68 (1.5)	-

5.3.2.4 Efficacy Results – Long Term Efficacy

Long term efficacy results of the following parameters are presented including a median follow-up duration of 22.6 months, which includes the time-to-event analyses for patients who entered the maintenance period and follow-up period. As of the cut-off date, 13 patients (6/70 [8.6%] in the CT-P10 group, 7/70 [10.0%] in the Rituxan® group) completed the maintenance period (Maintenance Cycle 12); the patients who were still ongoing the maintenance period have completed at least 10 months of the maintenance period. The total median follow-up duration was 22.8 and 22.0 months for CT-P10 and Rituxan® groups, respectively.

Duration of Response (CR, CRu or PR)

Response duration is measured from the time of the first response (CR, CRu or PR) until the first documentation of relapse or progression (Figure 50). The number of events among responders was 13/67 (19.4%) and 13/61 (21.3%) in the CT-P10 and Rituxan® groups, respectively (HR 1.11; 95% CI [0.47, 2.62], log-rank p-value 0.997). There was no significant difference in duration of response (CR, CRu or PR) between the treatment groups.



Note: Median follow-up of 22.6 months on July 31, 2017, cut-off date (including ≥10 months on monotherapy treatment).

Figure 50: Kaplan-Meier Plot of Overall Response (CR, CRu or PR) Duration in Study CT-P10 3.3: ITT Population - Local Review

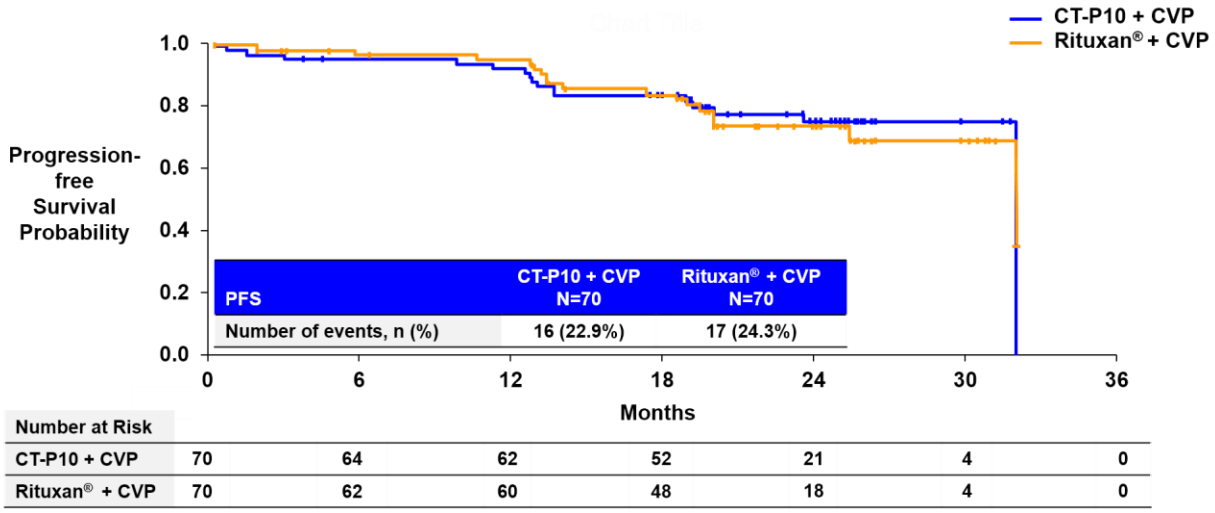
The duration of complete response (CR or CRu) was also examined. Of the patients who achieved CR or CRu (25 patients per treatment group), only 1 patient in the CT-P10 group and 2 patients in the Rituxan® group had disease progression during the treatment period. The log-rank p-value was 0.168. Although the dataset is relatively limited, the response in patients with CR or CRu was sustained in the most patients to date with similar proportions of patients between the treatment groups.

Progression-free Survival and Overall Survival

The PFS and OS results support the similar efficacy of CT-P10 and Rituxan® during the induction period with combination therapy and provide evidence of comparable and sustained efficacy during the maintenance period with rituximab monotherapy (CT-P10 or Rituxan® only) (Figure 51 and Figure 52).

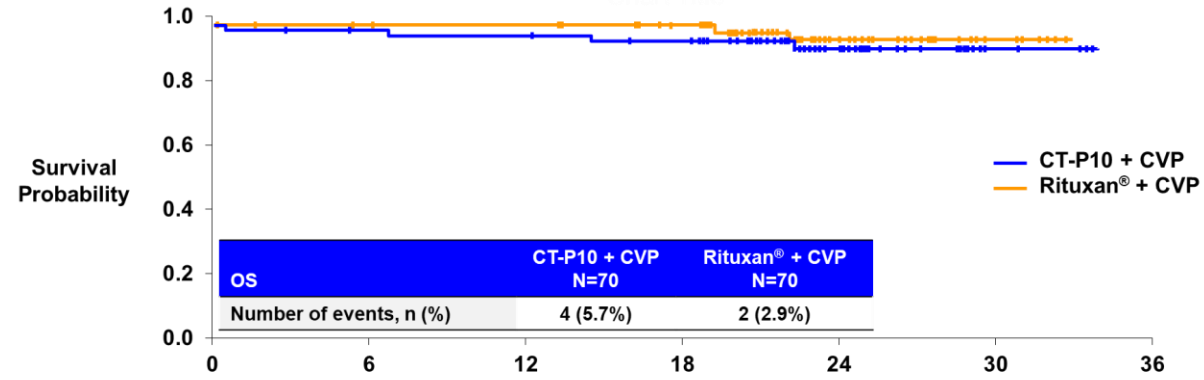
For PFS, events (disease progression or death from any cause) occurred in 16/70 (22.9%) and 17/70 (24.3%) patients in the CT-P10 and Rituxan® groups, respectively (HR 1.20; 95% CI [0.55, 2.61], log-rank p-value 0.806). The median survival rates of PFS for both groups were estimable for the current analysis, however, it was driven by only few progression events at the latest time point of the analysis.

With regard to OS, as of the cut-off date, 4/70 (5.7%) and 2/70 (2.9%) patients in the CT-P10 and Rituxan® groups, respectively, have died. The log-rank p-value was 0.464. Whilst descriptively a comparable number of events was detected, the number of patients with the event was not sufficient to estimate a statistically reliable HR and corresponding CI.



Note: Median follow-up of 22.6 months on July 31, 2017, cut-off date (including ≥10 months on monotherapy treatment).

Figure 51: Kaplan-Meier Plot of Progression Free Survival in Study CT-P10 3.3: ITT Population – Local Review



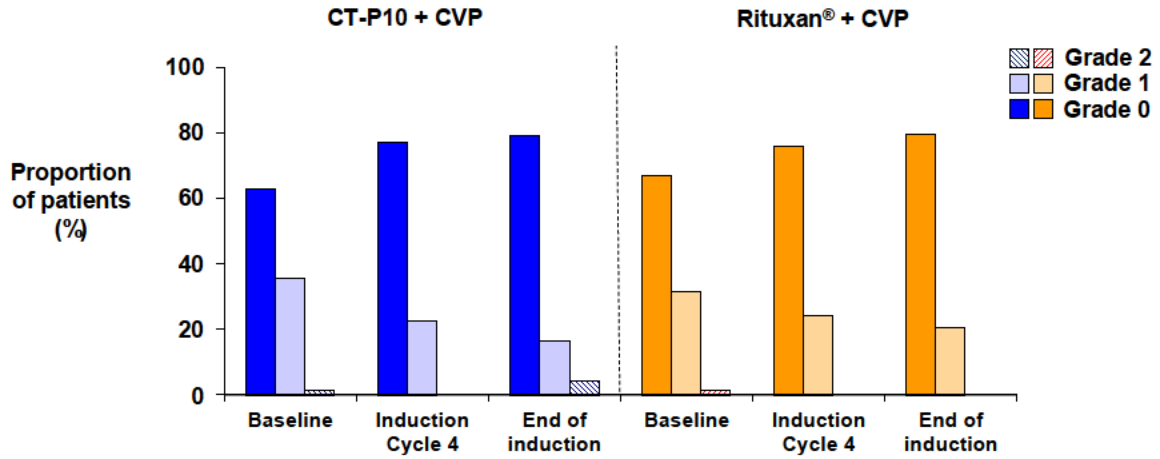
Number at Risk							
CT-P10 + CVP	70	67	66	63	28	4	0
Rituxan® + CVP	70	67	66	60	25	6	0

Note: Median follow-up of 22.6 months on July 31, 2017 cut-off date (including ≥10 months on monotherapy treatment).

Figure 52: Kaplan-Meier Plot of Overall Survival in Study CT-P10 3.3: ITT Population – Local Review

5.3.2.5 Performance Related Assessments

The ECOG performance status is one of the instruments that describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) and assess how progressing disease or anti-tumour therapy impact the daily life of patient. The ECOG performance status is shown for Study CT-P10 3.3 (Figure 53). At screening, the number of patients who had ECOG performance status of 0 were 44/70 (62.9%) and 47/70 (67.1%) in CT-P10 and Rituxan® groups, respectively; these rates were increased during the induction period (53/70 [75.7%] and 54/70 [77.1%] patients in CT-P10 and Rituxan® groups, respectively, at EOT1). For ECOG performance status of 1, decreases in the proportions of patients are shown in both treatment groups during the induction period.



Note: Assessable patients used as a denominator.
End of induction visit was to occur in the Induction Period 3 weeks (±3 days) after the last dose of CT-P10 or Rituxan® including early discontinued patients.
Grade 0: Fully active, able to carry on all pre-disease performance without restriction.
Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

Figure 53: The ECOG Performance Status in Study CT-P10 3.3

5.3.3 Clinical Efficacy Conclusions

The CT-P10 clinical development program included 2 comparative FL studies designed to confirm that there were no clinically meaningful differences between CT-P10 and Rituxan® in the Proposed Indications (Section 1.1).

Study CT-P10 3.4 demonstrated therapeutic equivalence between CT-P10 and Rituxan® as monotherapy in the first-line treatment of LTBFL based on the primary endpoint, 7-month BOR. The 2-sided 90% CI for the difference between CT-P10 and Rituxan® was entirely within the equivalence margin (±17%) agreed upon with the FDA.

Non-inferiority of ORR over 8 cycles (24 weeks) of R-CVP induction treatment has been established in Study CT-P10 3.3 in patients with advanced FL. The lower bound of 95% CI of the difference of overall response rate during the R-CVP induction period was on the positive side of the non-inferiority margin of -7%. In addition, efficacy results from the ongoing monotherapy maintenance period, demonstrated that responses were durable and sustained, with comparable results observed for CT-P10 and Rituxan®. Time-to-event analyses showed a small but comparable number of events between the treatment groups and no discernable differences for duration of response, PFS and OS.

In conclusion, the efficacy data from CT-P10 clinical studies support the clinical similarity of CT-P10 and Rituxan® for the Proposed Indications (Section 1.1).

5.4 Clinical Safety and Immunogenicity Results

5.4.1 Safety

Across all CT-P10 studies, inclusion/exclusion criteria and screening procedures were developed in accordance with the Rituxan® USPI (2018). Safety was assessed by immunogenicity testing, immunoglobulin (IgM, IgG, and IgA) testing, hypersensitivity monitoring via electrocardiograms and vital sign measurements (including blood pressure, heart and respiratory rates, and temperature), vital sign measurements, electrocardiograms, physical examination findings, AEs, SAEs, AESI (which included infections, infusion-related reactions [IRRs], anaphylaxis, and progressive multifocal leukoencephalopathy [PML]), clinical laboratory analyses, pregnancy testing, and concomitant medications. Signs and symptoms of tuberculosis were monitored throughout the study. All patients were screened for current or past diagnosis of tuberculosis, hepatitis B, hepatitis C, and human immunodeficiency virus. Patients with active and serious ongoing infections were not eligible for study entry.

The safety population included data from all patients who received at least 1 (full or partial) dose of the study drug.

As agreed with the FDA, the safety data from LTBFL and advanced FL patients are the most relevant for the Proposed Indications (Section 1.1) and thus are specifically discussed here. The safety in LTBFL and advanced FL patients is presented separately due to the impact of CVP therapy on occurrence of AEs. Safety results from Study CT-P10 3.4 in LTBFL patients include data collected over 7 months. Safety results from Study CT-P10 3.3 in advanced FL patients include data collected from the completed R+CVP induction period (up to 24 weeks) and ongoing monotherapy maintenance period (by clinical cut-off date of July 31, 2017, including median follow-up data of 22.6 months and maintenance period of ≥ 10 months). For FL studies (Studies CT-P10 3.4 and CT-P10 3.3), additional data for SAEs and death up to the cut-off date of February 23, 2018 are provided in order to cover the latest safety information.

5.4.1.1 Safety Results Overview

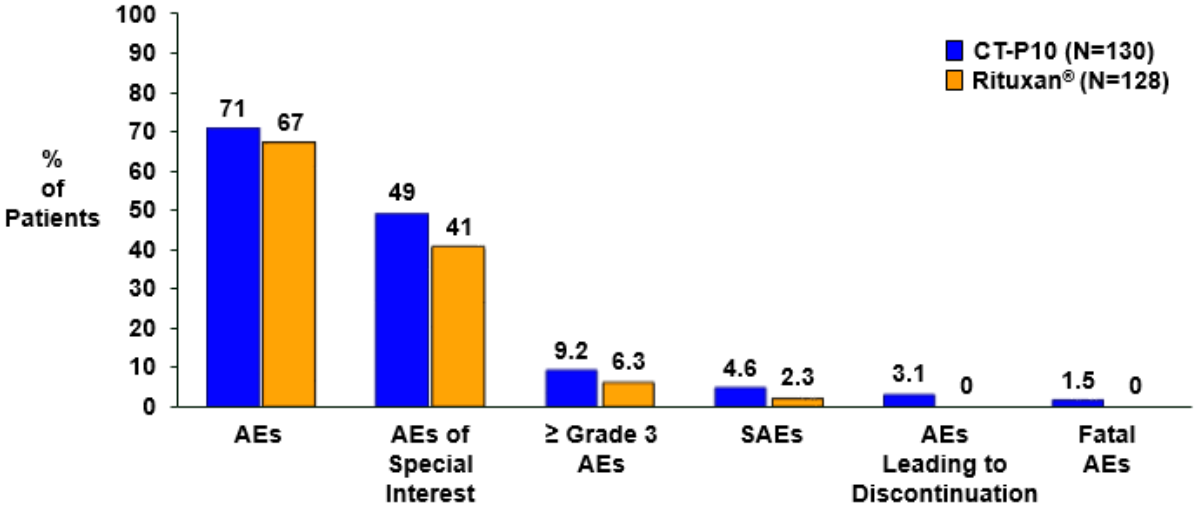
The FDA guidance document, *Scientific considerations in demonstrating biosimilarity to a reference Product* (2015), states: “Clinically meaningful differences could include a difference in the expected range of safety, purity, or potency of the proposed product and the reference product. By contrast, slight differences in rates of occurrence of certain AEs between the two products ordinarily would not be considered clinically meaningful differences.” Biosimilar studies are not powered for safety and therefore numerical differences in distribution of AEs are expected and should be interpreted in the context of epidemiological and disease characteristics, background chemotherapy, and the relatively small size of studies. The safety profile of CT-P10 was consistent with the known safety profile of Rituxan®, as described in the Rituxan® USPI (2018). Importantly, there were no new safety signals detected across the entire safety database.

Across both FL studies some numerical differences were observed. However, there was no specific pattern to these differences between CT-P10 and Rituxan®. Based on the strength of the analytical similarity between CT-P10 and Rituxan® and upon the systematic and detailed safety assessments,

it was concluded that these numerical differences are not clinically significant. The safety results derived from the main portions of the CT-P10 FL studies are summarized in Table 23. As expected, the occurrence of AEs and SAEs during monotherapy maintenance period of Study CT-P10 3.3 was considerably lower than during the CVP induction treatment period. The incidence of AEs, fatal AEs, grade ≥3 AEs, SAEs, AEs leading to permanent study drug discontinuation, and AESI were comparable between CT-P10 and Rituxan® groups across both LTBFL and advanced FL studies.

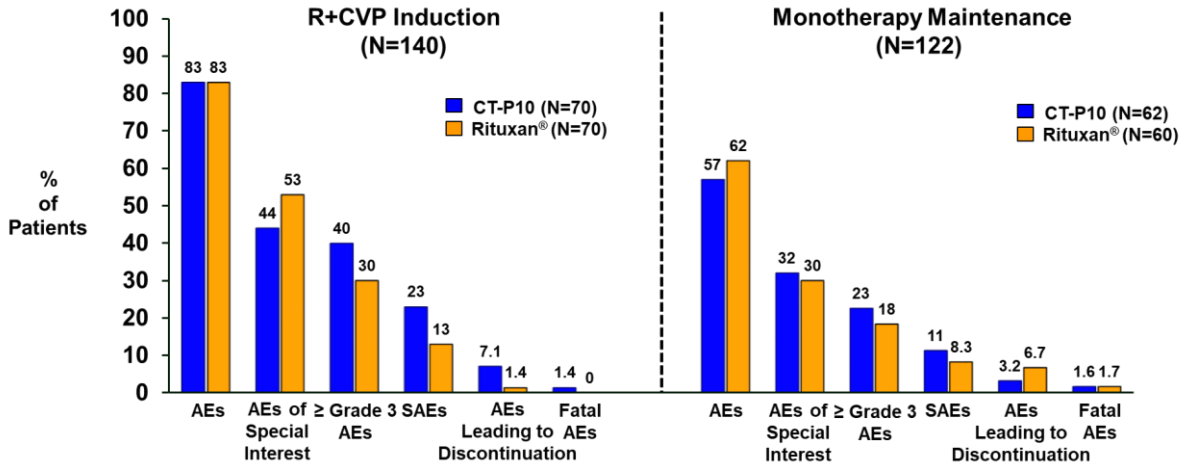
Table 23: Overview of Adverse Events in the FL Studies (Studies CT-P10 3.4 and CT-P10 3.3): Safety Population

Adverse Event Category Subcategory	Study CT-P10 3.4		Study CT-P10 3.3					
			Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=130)	Rituxan® (N=128)	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 +CVP (N=70)	Rituxan® +CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients							
SAEs	**6 (4.6)**	**3 (2.3)**	**21 (30.0)**	**13 (18.6)**	**16 (22.9)**	**9 (12.9)**	**7 (11.3)**	**5 (8.3)**
Fatal AEs	2 (1.5)	0	2 (2.9)	1 (1.4)	1 (1.4)	0	1 (1.6)	1 (1.7)
SAEs related to study drug	2 (1.5)	0	7 (10.0)	6 (8.6)	6 (8.6)	4 (5.7)	1 (1.6)	2 (3.3)
AEs	**92 (70.8)**	**86 (67.2)**	**63 (90.0)**	**60 (85.7)**	**58 (82.9)**	**58 (82.9)**	**35 (56.5)**	**37 (61.7)**
AEs related to study drug	64 (49.2)	51 (39.8)	40 (57.1)	38 (54.3)	37 (52.9)	36 (51.4)	12 (19.4)	13 (21.7)
AEs leading to permanent study drug discontinuation	4 (3.1)	0	7 (10.0)	5 (7.1)	5 (7.1)	1 (1.4)	2 (3.2)	4 (6.7)
Grade ≥ 3 AEs	12 (9.2)	8 (6.3)	36 (51.4)	27 (38.6)	28 (40.0)	21 (30.0)	14 (22.6)	11 (18.3)
AEs of Special Interest (AESI)	**63 (48.5)**	**52 (40.6)**	**35 (50.0)**	**41 (58.6)**	**31 (44.3)**	**37 (52.9)**	**20 (32.3)**	**18 (30.0)**
Infection	35 (26.9)	27 (21.1)	31 (44.3)	32 (45.7)	23 (32.9)	27 (38.6)	20 (32.3)	18 (30.0)
Infusion-related reaction	40 (30.8)	37 (28.9)	16 (22.9)	19 (27.1)	16 (22.9)	19 (27.1)	1 (1.6)	2 (3.3)
Anaphylaxis	0	0	1 (1.4)	0	1 (1.4)	0	0	0
PML	0	0	0	0	0	0	0	0



Note: Cut-off of 7 months assessment.

Figure 54: Overview of Adverse Events in LTBFL Study (Study CT-P10 3.4): Safety Population



Note: Median follow-up of 22.6 months on July 31, 2017 cut-off date (including ≥10 months on monotherapy treatment).

Figure 55: Overview of Adverse Events in Advanced FL Study (Study CT-P10 3.3): Safety Population

5.4.1.2 SAEs

Overall, no clinically meaningful differences were observed between the treatment groups in the incidence of SAEs. There were no discernable trends between the treatment groups in terms of SAEs by system organ class or preferred term (PT) and any observed numerical differences did not follow any specific pattern. The reported SAEs were consistent with the safety profile presented in the Rituxan® USPI (2018).

Table 24 and Table 25 show the incidence of SAEs by treatment group in the LTBFL and advanced FL studies, respectively, by PT. Additional data on SAEs up to the cut-off date of February 23, 2018 are provided in Appendix 2 (Table 37 and Table 38).

In the LTBFL study, no SAEs were reported in more than 1 patient (Table 24).

In the advanced FL study, the SAEs that were reported in more than 1 patient were febrile neutropenia, neutropenia, pneumonia, upper and lower respiratory tract infection and chronic obstructive pulmonary disease (Table 25).

Table 24: SAEs in LTBFL Study (Study CT-P10 3.4): Safety Population

Preferred Term	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Myocardial infarction	1 (0.8)	0
Constipation	1 (0.8)	0
Chest discomfort	1 (0.8)	0
Squamous cell carcinoma of lung	1 (0.8)	0
Abortion spontaneous	1 (0.8)	0
Respiratory failure	1 (0.8)	0
Gastrointestinal surgery	1 (0.8)	0
Pneumonia	0	1 (0.8)
Acute kidney injury	0	1 (0.8)
Genital prolapse	0	1 (0.8)

Table 25: SAEs in Advanced FL Study (Study CT-P10 3.3): Safety Population

Preferred Term	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Pneumonia	4 (5.7)	1 (1.4)	3 (4.3)	0	1 (1.6)	1 (1.7)
Febrile neutropenia	2 (2.9)	3 (4.3)	2 (2.9)	2 (2.9)	0	1 (1.7)
Chronic obstructive pulmonary disease	2 (2.9)	1 (1.4)	2 (2.9)	1 (1.4)	0	1 (1.7)
Lower respiratory tract infection	1 (1.4)	3 (4.3)	1 (1.4)	1 (1.4)	0	2 (3.3)
Neutropenia	1 (1.4)	1 (1.4)	1 (1.4)	0	0	1 (1.7)
Anemia	1 (1.4)	0	1 (1.4)	0	0	0
Pancytopenia	1 (1.4)	0	1 (1.4)	0	0	0
Atrial fibrillation	1 (1.4)	0	1 (1.4)	0	0	0
Constipation	1 (1.4)	0	1 (1.4)	0	0	0
Small intestinal perforation	1 (1.4)	0	1 (1.4)	0	0	0
Cholecystitis	1 (1.4)	0	1 (1.4)	0	0	0
Anaphylactic shock	1 (1.4)	0	1 (1.4)	0	0	0
Abdominal infection	1 (1.4)	0	1 (1.4)	0	0	0
Appendicitis	1 (1.4)	0	0	0	1 (1.6)	0
Campylobacter gastroenteritis	1 (1.4)	0	1 (1.4)	0	0	0
Post procedural fistula	1 (1.4)	0	1 (1.4)	0	0	0
Liver function test abnormal	1 (1.4)	0	1 (1.4)	0	0	0
Hypoalbuminemia	1 (1.4)	0	1 (1.4)	0	0	0
Hypocalcemia	1 (1.4)	0	1 (1.4)	0	0	0
Hypomagnesemia	1 (1.4)	0	1 (1.4)	0	0	0
Tumor lysis syndrome	1 (1.4)	0	1 (1.4)	0	0	0
Prostate cancer metastatic	1 (1.4)	0	0	0	1 (1.6)	0
Pleural effusion	1 (1.4)	0	1 (1.4)	0	0	0
Pulmonary embolism	1 (1.4)	0	1 (1.4)	0	0	0
Deep vein thrombosis	1 (1.4)	0	1 (1.4)	0	0	0
Hypertension	1 (1.4)	0	1 (1.4)	0	0	0

Preferred Term	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Sialoadenitis	1 (1.4)	0	0	0	1 (1.6)	0
Fracture	1 (1.4)	0	0	0	1 (1.6)	0
Injury	1 (1.4)	0	0	0	1 (1.6)	0
Adenocarcinoma gastric	1 (1.4)	0	0	0	1 (1.6)	0
Upper respiratory tract infection	0	2 (2.9)	0	0	0	2 (3.3)
Leukopenia	0	1 (1.4)	0	1 (1.4)	0	0
Diarrhea	0	1 (1.4)	0	1 (1.4)	0	0
Ileus	0	1 (1.4)	0	1 (1.4)	0	0
Pyrexia	0	1 (1.4)	0	1 (1.4)	0	0
Encephalitis	0	1 (1.4)	0	1 (1.4)	0	0
Subdural hematoma	0	1 (1.4)	0	1 (1.4)	0	0
Thrombophlebitis	0	1 (1.4)	0	1 (1.4)	0	0
Tachycardia	0	1 (1.4)	0	0	0	1 (1.7)
Peripheral ischemia	0	1 (1.4)	0	0	0	1 (1.7)

5.4.1.3 Adverse Events by Severity

The incidence of grade ≥ 3 AEs was comparable between CT-P10 and Rituxan® across both FL studies, as shown in Table 26. In LTBFL patients, the most common grade ≥3 AEs by PT (in either of the CT-P10 and Rituxan® groups, respectively) were neutropenia (1/130 [0.8%] patient and 1/128 [0.8%] patient in CT-P10 and Rituxan® groups, respectively) and neutrophil count decreased (2/130 [1.5%] patients and 0/128 patient in CT-P10 and Rituxan® groups, respectively).

In advanced FL patients, the most common grade ≥ 3 AEs by PT (in either of the CT-P10 and Rituxan® groups, respectively) were neutropenia (22/70 [31.4%] patients and 12/70 [17.1%] patients in CT-P10 and Rituxan® groups, respectively) and pneumonia (5/70 [7.1%] patients and 1/70 [1.4%] patient in CT-P10 and Rituxan® groups, respectively).

Table 26: Summary of Adverse Events by Severity in FL Studies (CT-P10 3.4 and CT-P10 3.3): Safety Population

Adverse Event Category Subcategory	Study CT-P10 3.4		Study CT-P10 3.3					
			Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=130)	Rituxan® (N=128)	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 +CVP (N=70)	Rituxan® +CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients							
AEs	**92 (70.8)**	**86 (67.2)**	**63 (90.0)**	**60 (85.7)**	**58 (82.9)**	**58 (82.9)**	**35 (56.5)**	**37 (61.7)**
Grade 1 AE	17 (13.1)	15 (11.7)	5 (7.1)	3 (4.3)	8 (11.4)	5 (7.1)	2 (3.2)	9 (15.0)
Grade 2 AE	63 (48.5)	63 (49.2)	22 (31.4)	30 (42.9)	22 (31.4)	32 (45.7)	19 (30.6)	17 (28.3)
Grade 3 AE	10 (7.7)	6 (4.7)	26 (37.1)	20 (28.6)	22 (31.4)	15 (21.4)	10 (16.1)	9 (15.0)
Grade 4 AE	0	2 (1.6)	8 (11.4)	6 (8.6)	5 (7.1)	6 (8.6)	3 (4.8)	1 (1.7)
Grade 5 AE	2 (1.5)	0	2 (2.9)	1 (1.4)	1 (1.4)	0	1 (1.6)	1 (1.7)

5.4.1.4 Deaths

Comparable numbers of deaths, including deaths due to disease progression or due to AEs in CT-P10 and Rituxan® groups were reported across CT-P10 FL studies. In total, 14 deaths were reported in Studies CT-P10 3.3 and CT-P10 3.4 in FL patients, including 7 deaths due to AEs reported up to February 23, 2018. These included 3 deaths (2 deaths in the CT-P10 group and 1 death in the Rituxan® group) in Study CT-P10 3.4 and 4 deaths (3 deaths in the CT-P10 group and 1 death in the Rituxan® group) in Study CT-P10 3.3. Of the 7 deaths, 3 were considered by the investigator to have possible relationship with study drug; 1 death due to myocardial infarction in a LTBFL patient treated with CT-P10, 1 death due to pneumonia in a LTBFL patient treated with Rituxan® and 1 death due to tumor lysis syndrome (TLS) in an advanced FL patient treated with CT-P10. The other 4 fatal AEs (respiratory failure in the CT-P10 group in Study CT-P10 3.4, gastric adenocarcinoma in the CT-P10 group in Study CT-P10 3.3, leukemic liver infiltration in the CT-P10 group in Study CT-P10 3.3, and respiratory tract infection in the Rituxan® group in Study CT-P10 3.3) were considered by the investigator to be unrelated to CT-P10 or Rituxan®. In addition, 7 additional deaths (5 deaths attributed to disease progression [3 deaths in the CT-P10 group and 2 deaths in the Rituxan® group], 1 death attributed to septic shock in the CT-P10 group and 1 death attributed to multiple organ failure in the Rituxan® group) occurred during the follow-up period in Study CT-P10 3.3.

Narratives of deaths were tabulated and provided in Appendix 3.

All deaths were reviewed by the DSMB. No concerns or new safety signals have been identified over the course of regular reviews of all studies.

5.4.1.5 Adverse Events

The incidence of AEs in FL studies was comparable between CT-P10 and Rituxan® groups. The type and severity of AEs were consistent with the safety profile of Rituxan® in NHL patients (Rituxan® USPI, 2018). AEs with an incidence of 5% or greater in either treatment group are shown in Table 27 and Table 28 for LTBFL and advanced FL studies, respectively.

The most frequently reported AEs in the LTBFL study (Study CT-P10 3.4) were IRR and upper respiratory tract infection. In the advanced FL study (Study CT-P10 3.3), the most frequently reported AEs were neutropenia and IRR.

Table 27: AEs (≥ 5% of Patients in Either Treatment Group) in LTBFL Study (Study CT-P10 3.4): Safety Population

Preferred Term	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Infusion related reaction	40 (30.8)	37 (28.9)
Upper respiratory tract infection	16 (12.3)	14 (10.9)
Fatigue	9 (6.9)	12 (9.4)
Diarrhea	7 (5.4)	6 (4.7)
Nausea	6 (4.6)	7 (5.5)

Table 28: AEs (≥ 5% of Patients in Either Treatment Group) in Advanced FL Study (Study CT-P10 3.3): Safety Population

Preferred Term	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Neutropenia	28 (40.0)	20 (28.6)	26 (37.1)	17 (24.3)	5 (8.1)	7 (11.7)
Infusion related reaction	16 (22.9)	19 (27.1)	16 (22.9)	19 (27.1)	1 (1.6)	2 (3.3)
Upper respiratory tract infection	13 (18.6)	18 (25.7)	6 (8.6)	14 (20.0)	10 (16.1)	9 (15.0)
Constipation	12 (17.1)	10 (14.3)	12 (17.1)	9 (12.9)	0	1 (1.7)
Neuropathy peripheral	10 (14.3)	12 (17.1)	10 (14.3)	12 (17.1)	1 (1.6)	1 (1.7)
Alopecia	10 (14.3)	5 (7.1)	10 (14.3)	5 (7.1)	0	0
Abdominal pain	8 (11.4)	10 (14.3)	6 (8.6)	10 (14.3)	2 (3.2)	0
Nausea	8 (11.4)	7 (10.0)	7 (10.0)	5 (7.1)	1 (1.6)	2 (3.3)
Arthralgia	7 (10.0)	4 (5.7)	4 (5.7)	4 (5.7)	3 (4.8)	2 (3.3)
Diarrhea	6 (8.6)	8 (11.4)	5 (7.1)	5 (7.1)	1 (1.6)	3 (5.0)
Fatigue	6 (8.6)	8 (11.4)	5 (7.1)	6 (8.6)	2 (3.2)	2 (3.3)
Urinary tract infection	6 (8.6)	6 (8.6)	4 (5.7)	4 (5.7)	4 (6.5)	5 (8.3)
Anemia	6 (8.6)	5 (7.1)	5 (7.1)	4 (5.7)	1 (1.6)	1 (1.7)
Lower respiratory tract infection	6 (8.6)	4 (5.7)	5 (7.1)	1 (1.4)	3 (4.8)	3 (5.0)
Pneumonia	6 (8.6)	3 (4.3)	5 (7.1)	2 (2.9)	1 (1.6)	1 (1.7)
Myalgia	6 (8.6)	2 (2.9)	4 (5.7)	2 (2.9)	2 (3.2)	0
Hypoesthesia	6 (8.6)	2 (2.9)	5 (7.1)	0	1 (1.6)	2 (3.3)
Cough	5 (7.1)	5 (7.1)	1 (1.4)	4 (5.7)	4 (6.5)	4 (6.7)
Edema	5 (7.1)	3 (4.3)	3 (4.3)	2 (2.9)	2 (3.2)	1 (1.7)
Hypertension	5 (7.1)	2 (2.9)	4 (5.7)	1 (1.4)	1 (1.6)	1 (1.7)
Fracture	5 (7.1)	1 (1.4)	0	1 (1.4)	5 (8.1)	0
Asthenia	4 (5.7)	7 (10.0)	3 (4.3)	6 (8.6)	1 (1.6)	3 (5.0)

Preferred Term	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Headache	4 (5.7)	5 (7.1)	3 (4.3)	3 (4.3)	1 (1.6)	2 (3.3)
Dizziness	4 (5.7)	4 (5.7)	1 (1.4)	2 (2.9)	3 (4.8)	2 (3.3)
Sinusitis	4 (5.7)	2 (2.9)	3 (4.3)	1 (1.4)	0	2 (3.3)
Dyspnea	4 (5.7)	1 (1.4)	3 (4.3)	1 (1.4)	1 (1.6)	0
Paresthesia	3 (4.3)	8 (11.4)	3 (4.3)	8 (11.4)	1 (1.6)	0
Pyrexia	3 (4.3)	6 (8.6)	2 (2.9)	6 (8.6)	1 (1.6)	0
Back pain	2 (2.9)	12 (17.1)	1 (1.4)	8 (11.4)	1 (1.6)	4 (6.7)
Insomnia	2 (2.9)	6 (8.6)	0	6 (8.6)	2 (3.2)	1 (1.7)
Hyperglycemia	2 (2.9)	5 (7.1)	0	5 (7.1)	2 (3.2)	0
Fungal infection	2 (2.9)	4 (5.7)	1 (1.4)	2 (2.9)	1 (1.6)	2 (3.3)
Influenza	2 (2.9)	4 (5.7)	2 (2.9)	1 (1.4)	0	3 (5.0)
Oropharyngeal pain	1 (1.4)	4 (5.7)	1 (1.4)	3 (4.3)	0	1 (1.7)
Stomatitis	1 (1.4)	4 (5.7)	1 (1.4)	4 (5.7)	0	1 (1.7)
Decreased appetite	0	6 (8.6)	0	6 (8.6)	0	0

5.4.1.6 AEs Leading to Permanent Study Drug Discontinuation

Overall, AEs that led to permanent study drug discontinuation were comparable among the treatment groups across both FL studies. Comparative analyses did not reveal any trends or new signals in the patients treated with CT-P10. Tabular presentation of all AEs leading to permanent study drug discontinuation is provided in Table 39 and Table 40 (Appendix 2) for LTBFL and advanced FL studies, respectively.

In the LTBFL study, 4/130 (3.1%) and 0/128 patients in the CT-P10 and Rituxan® groups discontinued due to AEs, respectively. No single AE leading to permanent study drug discontinuation was reported more than once per treatment group. In the advanced FL study, 7/70 (10.0%) and 5/70 (7.1%) patients in the CT-P10 and Rituxan® groups discontinued due to AEs, respectively. No single AE leading to permanent study drug discontinuation was reported more than once per treatment group.

5.4.1.7 Adverse Events of Special Interest

AESI included infections, IRR, anaphylaxis based on the criteria of Sampson *et al*., (2006) amnd PML. These AESIs were specified according to known safety risks of rituximab based on the Warnings and Precautions section of the Rituxan® USPI (2018). The incidences of AESIs in FL studies are presented in Section 5.4.1.1 (Table 23). There were no events of PML reported throughout the CT-P10 clinical program.

5.4.2 Immunogenicity

In the LTBFL, advanced FL and RA studies, immunogenicity was evaluated using both an immunoassay for the presence of ADAs and an assay for the presence of NAbs. These assays were validated in accordance with recommendations from the FDA guidance documents, *Immunogenicity Assessment for Therapeutic Protein Products* (2014) and *Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products* (2016).

Assessment for ADAs involved screening testing and, if positive, confirmatory testing. Samples that were confirmed positive by ADA assay underwent titer analysis and analysis for neutralizing capacity. The NAb assay also involved screening and confirmatory testing.

Immunogenicity was evaluated based on the safety population, which consisted of all patients who received at least 1 full or partial dose of the study drug (CT-P10, Rituxan® or MabThera®). All patients in the safety population were analyzed according to the treatment they received.

5.4.2.1 Study CT-P10 3.4 in Patients with LTBFL

The majority of patients had negative ADA test results in Study CT-P10 3.4. The rates of positive ADA and positive NAb were similar for CT-P10 and Rituxan® over 7 months (Table 29). The titer of ADA was low in the few ADA positive patients and there was no overt impact of ADA on PK, efficacy and safety of individual patients.

Table 29: ADA and NAb Results in Study CT-P10 3.4: Safety Population

Immunogenicity Test	CT-P10 (N=130)	Rituxan® (N=128)
	n (%)	
Screening		
ADA Positive	6 (4.6)	5 (3.9)
NAb Positive	0	0
Post-Treatment (Over 7 Months)		
At least one ADA Positive	1 (0.8)	3 (2.3)
At least one NAb positive	1 (0.8)	0

5.4.2.2 Study CT-P10 3.3 in Patients with Advanced FL

The majority of patients had negative ADA test results in Study CT-P10 3.3. The rates of positive ADA and positive NAb were comparable for CT-P10 and Rituxan® during the induction period and maintenance period (up to cut-off date of July 31, 2017, Table 30). The titer of ADA was low in the few ADA positive patients and there was no overt impact of ADA on PK, efficacy and safety of individual patients.

Table 30: ADA and NAb Results in Study CT-P10 3.3, Induction and Maintenance Period: Safety Population

Immunogenicity Test	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)
	n (%)	
Screening		
ADA Positive	5 (7.1)	8 (11.4)
NAb Positive	0	0
Post-Treatment (Induction and Maintenance Period)		
At least one ADA Positive	3 (4.3)	4 (5.7)
At least one NAb positive	2 (2.9)	2 (2.9)

5.4.2.3 Study CT-P10 3.2 in Patients with RA

Study CT-P10 3.2 – Main Period (48 Week)

Overall, the proportion of ADA-positive patients was comparable between the CT-P10 and reference product groups with a very low incidence of NAb during the main period of Study CT-P10 3.2. Most patients had a negative ADA test result at each time point. The ADA titer results were also low and comparable between the 3 treatment groups. The proportions of ADA positive samples at each time point up to Week 48 in Study CT-P10 3.2 are presented in Table 31 and Figure 56. ADA titer results at each time point are provided in Table 32 and Figure 57.

Table 31: ADA and NAb Results in Study CT-P10 3.2, Main Period: Safety Population

Immunogenicity Test (Pre-dose)	CT-P10 (N=161)	Rituxan® (N=151)	MabThera® (N=60)	Rituxan® + MabThera® (N=211)
	n (%)			
Week 0				
ADA Positive	19 (11.8)	13 (8.6)	7 (11.7)	20 (9.5)
NAb Positive	1 (0.6)	0	0	0
Week 24				
ADA Positive	24 (14.9)	33 (21.9)	16 (26.7)	49 (23.2)
NAb positive	0	1 (0.7)	0	1 (0.5)
Week 48				
ADA Positive	7 (4.3)	13 (8.6)	5 (8.3)	18 (8.5)
NAb positive	1 (0.6)	1 (0.7)	0	1 (0.5)

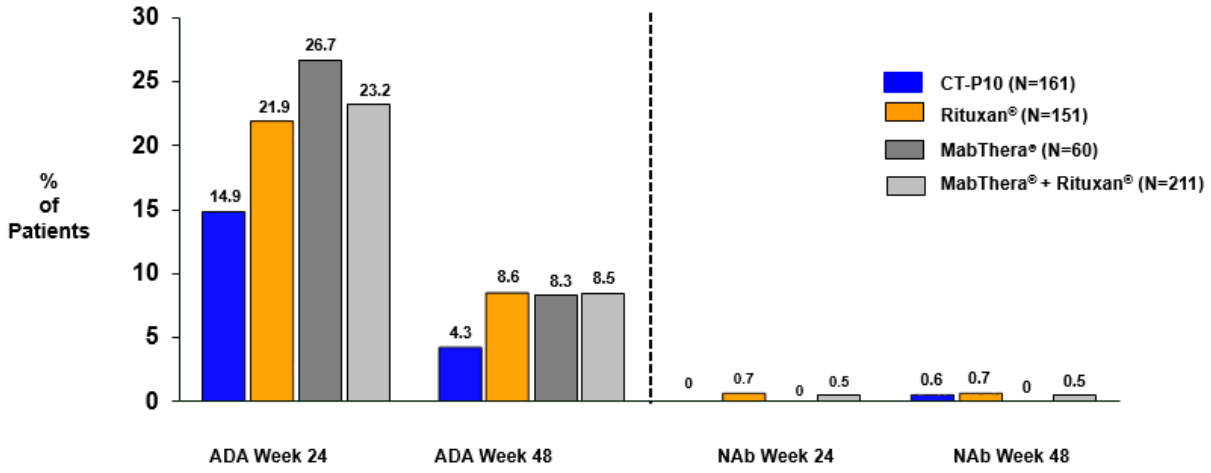


Figure 56: ADA and NAb Results in Study CT-P10 3.2, Main Period: Safety Population

Table 32: ADA Titer Results in Study CT-P10 3.2, Main Period: Safety Population

Immunogenicity Test (Pre-dose)	CT-P10	Rituxan®	MabThera®	Rituxan® + MabThera®
	Mean (± SD)			
Week 0	2.4 (± 2.03)	3.1 (± 1.66)	1.1 (± 0.38)	2.4 (± 1.64)
Week 24	3.8 (± 2.44)	3.7 (± 2.69)	3.6 (± 2.50)	3.7 (± 2.60)
Week 48	5.9 (± 4.85)	3.8 (± 3.09)	2.2 (± 0.84)	3.3 (± 2.72)

Note: The ADA titer values of the CT-P10 tagged assay were transformed using a $[\log_2(x)] + 1$ transformation.

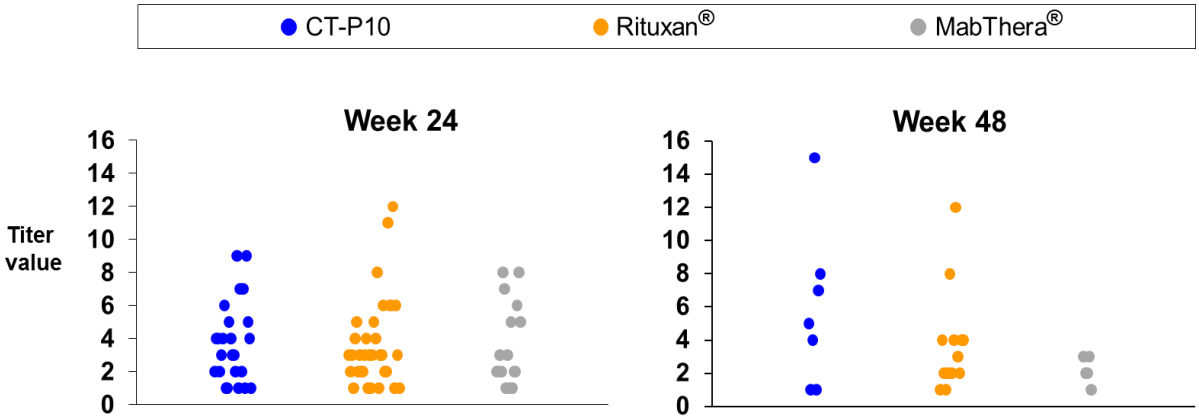


Figure 57: Individual ADA Titers in Study CT-P10 3.2, Main Period

Study CT-P10 3.2 – Extension Period

ADA and NAb test results from the extension period are summarized for the safety population in Table 33 for patients who transitioned to CT-P10 or continued on Rituxan® or CT-P10. Two patients (1 patient [1.6%] each in the Rituxan®/Rituxan® group and Rituxan®/CT-P10 group) had new positive ADA test results after the first infusion in the extension period; thus, no discernible change in ADA status following single transition was detected. Overall, the immunogenicity findings during the extension period were consistent with the results seen in the main period. The majority of patients were ADA negative at Week 72 with a very low incidence of NAb.

Table 33: ADA and NAb Results in Study CT-P10 3.2, Extension Period: Safety Population

Immunogenicity Test (Pre-dose)	CT-P10 /CT-P10 (N=122)	Rituxan® /Rituxan® (N=64)	Rituxan® /CT-P10 (N=62)	MabThera® /CT-P10 (N=47)
	n (%)			
Week 72				
ADA Positive	5 (4.1)	2 (3.1)	8 (12.9)	3 (6.4)
New ADA Positive	0	1 (1.6)	1 (1.6)	0
New NAb Positive	0	0	0	0

5.4.2.4 Study CT-P10 1.1/1.3 in Patients with Rheumatoid Arthritis

Overall, the proportion of patients with RA who had ADA positive results was comparable between the CT-P10 and Rituxan® groups at each time point, and the majority of these patients were NAb negative. The immunogenicity results following 2 courses of treatment are presented in Table 34.

Table 34: ADA and NAb Results in Study CT-P10 1.1: Safety Population

Immunogenicity Test (Pre-dose)	CT-P10	MabThera®
	n (%)	
1st Course	**(N=102)**	**(N=51)**
Week 0		
ADA Positive	23 (22.5)	7 (13.7)
NAb Positive	6 (5.9)	0
Week 24		
ADA Positive	18 (17.6)	9 (17.6)
NAb positive	2 (2.0)	1 (2.0)
2nd Course	**(N=60)**	**(N=23)**
Week 48		
ADA Positive	12 (20.0)	5 (21.7)
NAb Positive	1 (1.7)	1 (4.3)

In Study CT-P10 1.3, there was no new case of positive ADA following transition from MabThera® to CT-P10.

5.4.2.5 Impact of Antibody Status on PK, Efficacy and Safety

Impact of Anti-Drug Antibodies on PK

For this analysis, patients in the PK population who tested positive for ADA at Week 24 were considered the PK ADA-positive subgroup and those who tested negative were considered the PK ADA-negative subgroup. Analyses by ADA status showed that the development of ADAs influenced the PK profile of both CT-P10 and reference product, but this impact was comparable between both treatment groups.

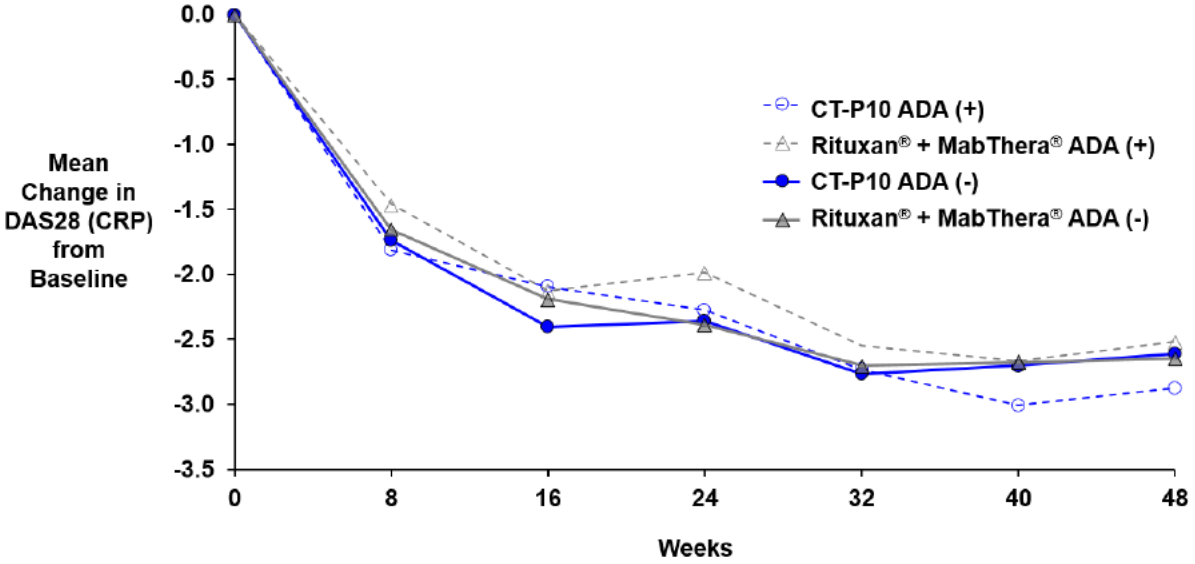
Results from Study CT-P10 3.2 are summarized in Table 35. These analyses are exploratory in nature and limited by the small sample sizes within subgroups, and were not intended to demonstrate equivalence on their own. The analyses indicate comparable trends for PK between CT-P10 and the reference product for both ADA-positive and ADA-negative categories, although the 90% CI for geometric LS means were outside of 80 - 125% range for the ADA-positive subgroup due to fragmented statistical power.

Table 35: Analysis of Primary PK Endpoints According to ADA Status in Study CT-P10 3.2

Treatment and Comparison	$AUC_{0\text{-last}}$ (h•µg/mL)	$AUC_{0\text{-inf}}$ (h•µg/mL)	C_{max} (µg/mL)
PK ADA-negative subgroup			
	Geometric LS Mean [Number of Patients]		
CT-P10	159306 [51]	155564 [49]	374 [51]
Rituxan®	168524 [46]	168732 [46]	393 [46]
	Ratio of Geometric LS Means (90% CI) (%)		
CT-P10 vs.Rituxan®	94.53 (85.70 - 104.27)	92.20 (83.69 - 101.56)	95.24 (89.08 - 101.82)
PK ADA-positive subgroup			
	Geometric LS Mean [Number of Patients]		
CT-P10	159039 [8]	174889 [7]	393 [8]
Rituxan®	122822 [14]	140042 [13]	321 [14]
	Ratio of Geometric LS Means (90% CI) (%)		
CT-P10 vs.Rituxan®	129.49 (93.80 - 178.74)	124.88 (90.13 - 173.03)	122.45 (87.10 - 172.16)

Impact of Anti-Drug Antibodies on Efficacy

The change from baseline in DAS28 (CRP) was assessed by post-treatment ADA status in Study CT-P10 3.2. There is no clear association between DAS28 change and ADA status and similar trends were observed between the CT-P10 and reference product group (Rituxan® + MabThera®) regardless of post-treatment ADA results (Figure 58).



Note: Patients who have at least one 'Positive' ADA result in Week 24 and Week 48 were defined as 'ADA Positive'.

Figure 58: Analysis of DAS28 (CRP) by Post-treatment ADA Status in Study CT-P10 3.2

Occurrence of IRRs and ADA Status

With regard to the effect of ADA on patient safety, the frequencies of IRRs were analyzed by ADA status. Results from the main RA study, Study CT-P10 3.2 are presented here.

During the main period in Study CT-P10 3.2 (up to Week 48), the incidence of IRRs in post-treatment ADA positive or negative patients were generally comparable between the CT-P10 and MabThera® groups with a slightly lower rate in the Rituxan® group (Table 36). During the extension period, 2 patients (1 patient [1.6%] each in the Rituxan®/Rituxan® group and Rituxan®/CT-P10 group) had new positive ADA test results after the Extension Week 0 infusion and no IRRs were reported for both patients.

Thus, no clinically significant differences in IRRs were observed in the Study CT-P10 3.2 between the treatment groups when analyzed by ADA status.

Table 36: Summary of IRRs by Post-treatment ADA Status in Study CT-P10 3.2, Main Period: Safety Population

	CT-P10 (N=161)	Rituxan® (N=151)	MabThera® (N=60)	Rituxan® + MabThera® (N=211)
	n/N' (%)			
The 1st Treatment Course				
ADA positive	4/24 (16.7)	0/33 (0.0)	3/16 (18.8)	3/49 (6.1)
ADA negative	18/121 (14.9)	5/108 (4.6)	8/42 (19.0)	13/150 (8.7)
The 2nd Treatment Course				
ADA positive	3/26 (11.5)	1/32 (3.1)	1/17 (5.9)	2/49 (4.1)
ADA negative	9/116 (7.8)	5/106 (4.7)	1/41 (2.4)	6/147 (4.1)

Note: Percentages were calculated using the number of patients in each ADA subgroup (N') as the denominator and the number of patients with at least 1 event of IRR (n) as the numerator.

5.4.3 Conclusion on Safety and Immunogenicity

The purpose of the safety assessment of a biosimilar product is to compare its safety profile to that of the reference product. The total safety database for CT-P10 in FL patients consists of 398 patients with FL who were exposed to CT-P10 and Rituxan®.

The safety risks identified in the CT-P10 clinical development program are consistent with the known AE profile of Rituxan®. There were no clinically meaningful differences observed between the CT-P10 and Rituxan® groups in FL patients with regards to the proportion of patients with AEs, fatal AEs, grade ≥3 AEs, SAEs, AEs leading to permanent study drug discontinuation and AESIs, known safety risks described in the USPI of Rituxan® (2018). Overall, the frequency and severity of these events were similar between the treatment groups and in line with safety characteristics reported in the Rituxan® USPI (2018). Development of anti-rituximab antibodies (in terms of rates of ADA and NAb and respective titers) was similar for CT-P10 and Rituxan®/MabThera® in both FL and RA patients. Notably, there was no increase in *de novo* ADA formation following single transition from the reference product to CT-P10 in patients with RA.

The safety data demonstrated that there are no clinically meaningful differences between CT-P10 and Rituxan® in the populations studied. Thus, it is concluded that the safety profile outlined in the Rituxan® USPI (2018) also applies to the use of CT-P10 in the Proposed Indications (Section 1.1).

6 EXTRAPOLATION OF INDICATIONS

In line with the FDA guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (2015), if the proposed product meets the statutory requirements for licensure as a biosimilar product, licensure for one or more additional conditions of use, for which the reference product is licensed, may be approved. Robust scientific justification for extrapolating clinical data is required for each indication and patient population for which approval is sought.

The systematic scientific justification for extrapolation is based on:

- A common MoA across NHL indications approved for Rituxan® (Rituxan® USPI, 2018)
- Understanding of the clinical pharmacology (PK/PD) in NHL indications approved for Rituxan® (Rituxan® USPI, 2018)
- Understanding of the immunogenicity and its clinical impact in the intended patient populations for the Proposed Indications (Section 1.1)
- Comparable safety profile between NHL conditions approved for Rituxan® (Rituxan® USPI, 2018) notwithstanding differences in AEs attributed to background chemotherapy

The comprehensive physicochemical and functional similarity data from analytical studies of CT-P10, Rituxan® and MabThera®, together with non-clinical and comparative clinical data in FL and RA patients, provide sufficient evidence to clearly demonstrate that CT-P10 and Rituxan® are similar in terms of safety, purity and potency. These data together with an extensive review of published literature, provide evidence to support extrapolation to the Proposed Indications and thus support licensure of CT-P10 for the Proposed Indications (Section 1.1).

The analytical, non-clinical, and clinical studies are intended solely to satisfy the statutory requirements for the licensure of a biosimilar application and are not intended to encourage the use of CT-P10 in any indication not included in CELLTRION's draft label.

6.1 Analytical Similarity

6.1.1 Mechanisms of Action and B-cell Pathology in NHL

The therapeutic effect of rituximab across different mature B cell non-Hodgkin's lymphomas is directly linked to CD20-binding and consequent effects on B-cells including depletion of B-cells, resulting in reduction of the tumor burden. Across NHL indications, B-cell depletion is driven by the binding of rituximab to the CD20 cell surface antigen on peripheral B-cells and subsequent induction of apoptosis, CDC, ADCC and/or ADCP. The biological activities of CT-P10 linked to these mechanisms have been demonstrated to be highly similar to Rituxan®.

The results of the physicochemical and structural similarity studies clearly demonstrate that CT-P10 is highly similar to Rituxan® and MabThera®, notwithstanding minor differences in clinically inactive components.

Furthermore, in comparison with Rituxan® and MabThera®, CT-P10 has highly similar biological properties, as demonstrated by the results of binding and cell-based assays. These studies showed:

- High similarity in CD20 binding;
- High similarity in Fc-mediated binding;
- High similarity in CDC, ADCC, ADCP and apoptosis which are related to the cited MoA of rituximab, to the extent the MoA of Rituxan® is known.

As well as demonstrating similarity, these data support that there are no clinically meaningful differences between CT-P10, Rituxan® and MabThera® in functional activities. Additional studies using B-cells from PBMC of individuals of different disease state showed comparable CDC, ADCC, ADCP and apoptosis induced by CT-P10, Rituxan® and MabThera®, further supporting similarity and an expectation that CT-P10 and Rituxan® will have the same therapeutic effect as Rituxan® in the Proposed Indications (Section 1.1).

6.2 Clinical Pharmacology

6.2.1 PK Similarity

Studies in NHL patients

The PK profile of Rituxan® following intravenous administration in each indication of use is well studied. The published PK data for Rituxan® are consistent between NHL indications. CELLTRION demonstrated PK similarity for CT-P10 and Rituxan® in Study CT-P10 3.3 in advanced FL patients under a repeated-cycle dosing regimen. The linear concentration-time profiles for Cycle 4 (Week 9-12) for CT-P10 and Rituxan® were nearly identical. Importantly, the PK data (C_{trough}) obtained in the CT-P10 advanced FL study are consistent with published C_{trough} results for intravenously administered rituximab in NHL patients (Genentech, Inc., 2017; Figure 59). Similar PK was also shown in Study CT-P10 3.4 in LTBFL patients under monotherapy treatment with rituximab.

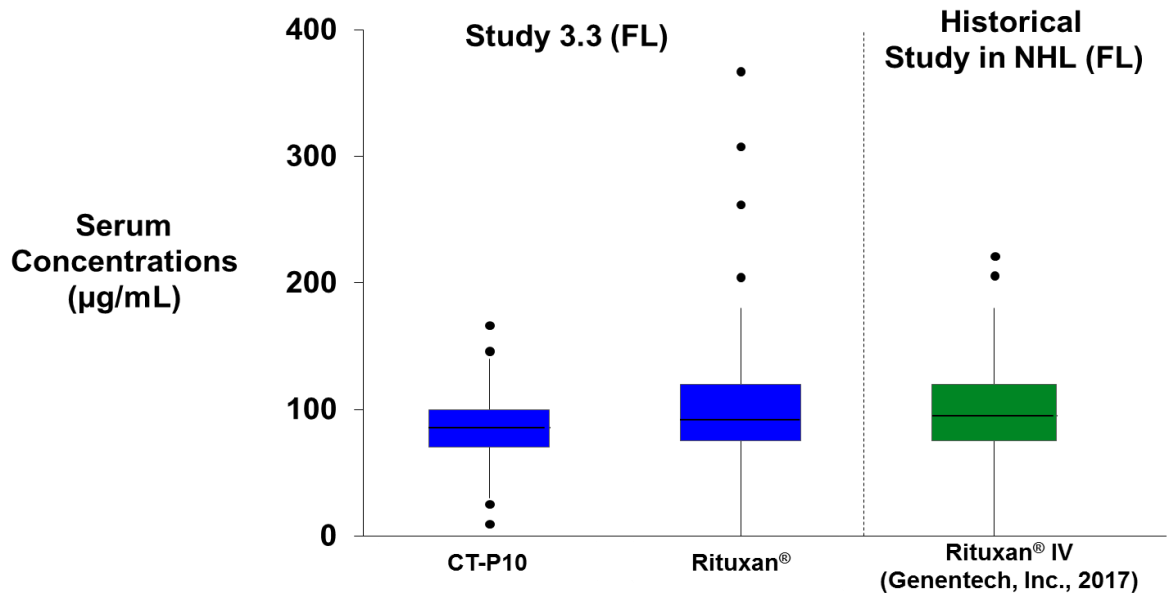


Figure 59: C_{trough} Levels from CT-P10 Study in Advanced FL Patients and Rituxan Treatment Group (Intravenously Administered Rituxan®) from a Historical Study with Rituxan® (Genentech, Inc., 2017)

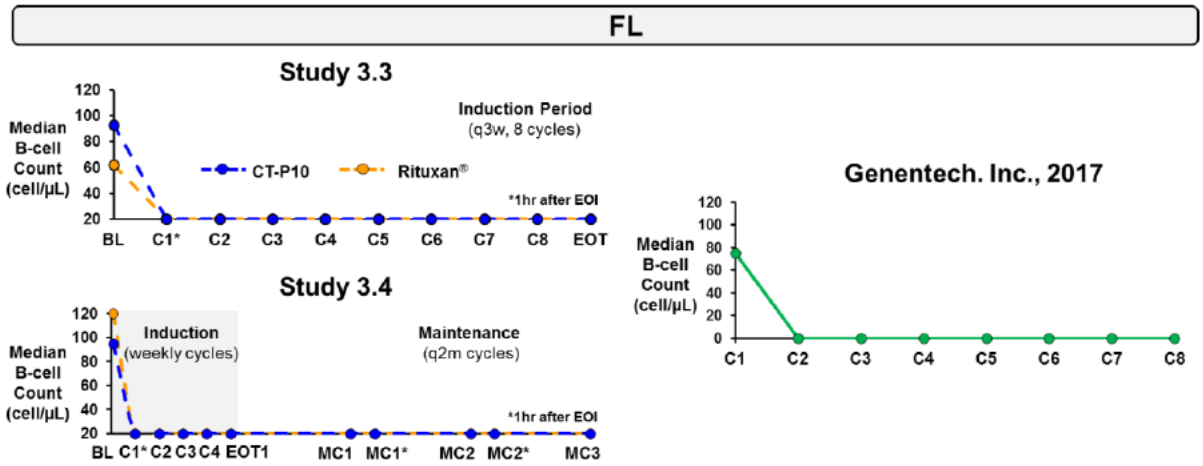
Studies in RA patients

The PK similarity between CT-P10, Rituxan® and MabThera® was demonstrated in Studies CT-P10 3.2 and CT-P10 1.1 in patients with RA. The linear concentration-time profiles up to Week 24 were nearly identical across the 3 products. Importantly, the PK data obtained in CT-P10 RA studies are consistent with published rituximab PK results in RA patients (Rituxan® USPI, 2018).

The comparative PK data in CT-P10 FL and RA studies, combined with the knowledge of the PK profiles of rituximab in different patient populations, indicate that CT-P10 will have a PK profile similar to that of Rituxan® in the Proposed Indications (Section 1.1).

6.2.2 PD Similarity

The PD profile following intravenous administration of Rituxan® has been well-studied in each indication of use. Intravenous administration of rituximab results in rapid and sustained B-cell depletion with limited recovery observed upon treatment completion or discontinuation. The pattern and durability of B-cell depletion following administration of rituximab is consistent between published Rituxan® NHL studies. In Study CT-P10 3.4, a similar pattern of B-cell depletion was induced by CT-P10 and Rituxan® in an LTBFL population. Study CT-P10 3.3 also demonstrated PD similarity between CT-P10 and Rituxan® in an advanced FL population based on B-cell counts over 8 cycles (24 weeks). The B-cell depletion observed in Study CT-P10 3.4 and Study CT-P10 3.3 to date align with those reported in published NHL studies of Rituxan® (Piro *et al.*, 1999; Genentech, Inc., 2017; Figure 60).



Note: For Study CT-P10 3.3, B-cell data are not evaluated per protocol during the Maintenance and Follow-up Periods.

Figure 60: Time Course of B-Cell Depletion in CT-P10 Studies and Historical Study with Rituxan® (Genentech, Inc., 2017)

The comparative PD data from the CT-P10 clinical program, combined with knowledge of the B-cell depleting effects of rituximab in different patient populations, strongly suggest that CT-P10 will display similar PD to Rituxan® in the Proposed Indications (Section 1.1).

6.3 Immunogenicity

The immunogenicity of Rituxan® has been published and reported across different conditions of use (Rituxan® USPI, 2018). Notably, the incidence of ADA is greater with Rituxan® in RA patients compared to patients with lymphoproliferative disorders. State-of-art validated and highly sensitive immunogenicity assays were developed in accordance with FDA guidance document, *Immunogenicity Assessment of Therapeutic Protein Products* (2014). Across all CT-P10 studies, FL and RA patients exhibited similar immunogenicity to both biosimilar and reference products, regardless of whether background chemotherapy (CVP in advanced FL patients) or immunomodulatory agents (MTX in RA patients) were used or not (monotherapy in LTBFL patients). The impact of immunogenicity on PK, efficacy and safety was similar between CT-P10, Rituxan® and MabThera® in all FL and RA studies. Therefore, the immunogenicity of CT-P10 can be expected to be similar to that of Rituxan® in the Proposed Indications (Section 1.1).

6.4 Safety

There is considerable safety and effectiveness experience with Rituxan®, including exposure in more than 4.4 million patients treated globally across all conditions of use. The well-characterized safety of Rituxan® across all licensed indications is generally consistent, notwithstanding some differences in distribution of AEs related to the use of background chemotherapies. As discussed in Section 5.4.1, no clinically meaningful differences in toxicities were observed between CT-P10 and Rituxan® in FL studies, and the AEs were consistent with the known safety profile of rituximab. The known risks associated with rituximab are common across licensed indications and dosing regimens. Given the similarity in the safety profiles of CT-P10 and Rituxan® in CT-P10 clinical studies, the safety profile of CT-P10 can be expected to be comparable to that of Rituxan® in the Proposed Indications (Section 1.1).

6.5 Other Factors That May Affect Safety or Efficacy

No clinically meaningful differences in PK, efficacy and safety were observed in CT-P10 clinical studies when analyzed by subgroups such as age, race, and gender. The demonstration of similar PK, efficacy and safety profiles for CT-P10 and Rituxan® across various subgroups in CT-P10 clinical studies supports the safety and efficacy in the Proposed Indications (Section 1.1). Given the demonstrated similarity between CT-P10 and Rituxan®, the impact of extrinsic factors (e.g., PK interactions with other chemotherapeutic treatments, concomitant therapies and radiotherapy, drug resistance and long-term treatment) is expected to be similar for CT-P10 and Rituxan® in the Proposed Indications (Section 1.1).

6.6 Conclusion

In accordance with FDA guidelines, CELLTRION has provided a robust scientific justification for each of the Proposed Indications contained in the draft label submitted with its May 29, 2018 BLA resubmission (Section 1.1).

No residual uncertainties based on MoA, PK/PD, immunogenicity and safety were identified that would preclude extrapolation from one indication to the Proposed Indications (Section 1.1). The comprehensive physicochemical and functional similarity data from analytical studies of CT-P10, Rituxan® and MabThera® together with comparative clinical studies in FL and RA patients, provide sufficient evidence to demonstrate that CT-P10 is similar to Rituxan® in terms of quality, safety and efficacy and that there are no clinically meaningful differences, supporting approval of CT-P10 for use in the Proposed Indications (Section 1.1).

7 OVERALL CONCLUSIONS

The FDA biosimilar guidance document, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (2015), outlines the approach for development and approval of a biosimilar product. A proposed biosimilar that is demonstrated to be biosimilar to a reference product can rely on the existing scientific knowledge about the safety, purity and potency reference biological product to support licensure. The emphasis on a biosimilar product development program focuses on the comparative evaluation of the biosimilar and reference product and the demonstration of similarity through structural and functional studies, limited non-clinical studies and targeted clinical studies, with each subsequent development stage addressing the residual uncertainty and clinical importance of prior results.

The analytical, non-clinical, and clinical studies conducted are intended solely to satisfy the statutory requirements for the licensure of a biosimilar application and are not intended to encourage use of CT-P10 in any indication not included in the draft label submitted by CELLTRION in May 2018.

The results of the analytic similarity studies demonstrate that CT-P10 is highly similar to Rituxan® in physicochemical structure and biological function. The *in vitro* analytical methods, representative of the reported modes of action of rituximab, demonstrate high similarity in functional activities. These data strongly support that CT-P10 can be expected to exert the same therapeutic effect as Rituxan®, supporting extrapolation to the Proposed Indications (Section 1.1).

Biosimilarity is also supported by results from the non-clinical studies, which showed similar exposure and toxicity between CT-P10 and MabThera®.

Finally, similarity of CT-P10 and Rituxan® in PK, PD, efficacy, safety and immunogenicity was demonstrated in 2 clinical studies in FL patients. Additional PK similarity and immunogenicity data were generated in 3 clinical studies in RA patients.

The totality of evidence from the CT-P10 biosimilar development program supports the conclusion that CT-P10 meets the scientific and statutory requirements for the demonstration of biosimilarity. Specifically, CT-P10 is analytically highly similar to Rituxan® notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between CT-P10 and Rituxan® in terms of PK, efficacy, safety and immunogenicity. Collectively, this body of evidence provides compelling justification for approval of CT-P10 as a biosimilar to Rituxan® for the Proposed Indications of:

- Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to CT-P10 in combination chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20- positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy

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Appendix 1 Additional Information on Analytical Methods and Results

A description of methods used in analytical similarity assessments and graphical data are provided below.

1. Physicochemical and Structural Assays

The following section provides a brief description of the state-of-the-art physicochemical and structural test methods used in 3-way analytic similarity studies and data from a subset of these test methods. All methods were appropriately validated or qualified and were determined to be suitable for their intended use.

1.1 Primary Structure

Peptide Mapping by HPLC

Samples were reduced, alkylated and digested and the resulting peptide fragments were separated by Reversed Phase - High Performance Liquid Chromatography (RP-HPLC). The peptide peaks were detected at 214 nm and 280 nm and data collected at 214 nm are used for evaluation. Peaks in the peptide map were integrated and relative peak area and absolute peak retention times were calculated and evaluated against those of the reference materials (Figure 12).

Peptide Mapping by LC-MS

Samples were analyzed by LC-MS peptide mapping after reduction, alkylation and proteolytic digestion. The resulting peptides were separated by reverse-phase ultra-performance liquid chromatography (RP-UPLC) using a column with a gradient of acetonitrile (Figure 61). An online mass spectrometer with an electrospray source was used to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis).

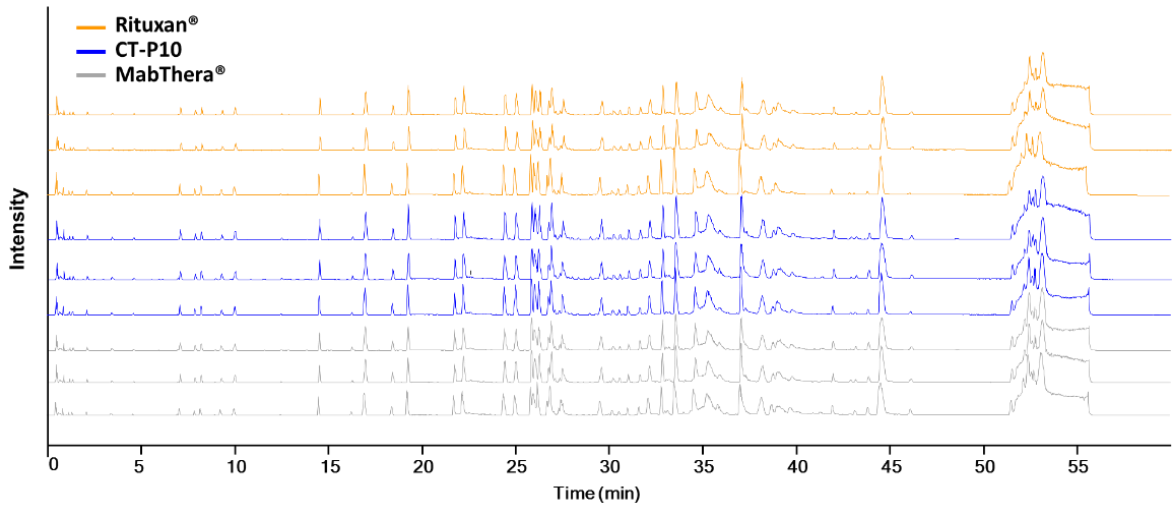


Figure 61: Total Ion Chromatograms of Peptide Mapping by LC-MS for Representative Lots of CT-P10, Rituxan® and MabThera®

Amino Acid Analysis and Molecular Absorptivity

Amino acid analysis was performed by hydrolysis of peptide bonds with 6 M HCl followed by pre-column derivatization using AQC reagent (6-aminoquinolyl-N-hydroxysuccinimidyl carbamate), separation by RP-HPLC and fluorescence detection.

Measurements of optical density at 280 nm (OD_{280}) were performed using a spectrophotometer. The Beer-Lambert equation was applied using the measured OD_{280} and protein molarity derived from the amino acid analysis described above. Protein concentration was determined with concentration of robust amino acids, those where the difference between theoretical ratio and observed ratio is < 5%. Molar extinction coefficient was calculated using UV absorbance at 280 nm, concentration of protein and molecular weight of samples.

N-terminal and C-terminal Sequencing

Samples were subjected to peptide mapping in combination with MS/MS to determine the N- and C-terminal sequence of the heavy and light chains.

The heavy and light chains were separated, alkylated, and desalted. Desalted samples were enzymatically digested. For N-terminal analysis, trypsin was used and for C-terminal analysis, Lys-C and trypsin were used for proteolytic digestion. The N-terminal and C-terminal peptides were separated by reversed-phase UPLC using a column with gradient of acetonitrile. An online mass spectrometer with an electrospray source was used to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing.

Intact Mass

The intact protein was eluted by reverse-phase HPLC using a column with gradient of acetonitrile. Intact mass by LC/MS was analyzed using an online TOF mass spectrometer with an electrospray source. The acquired mass spectra were then deconvoluted to intensity versus molecular mass (Figure 62).

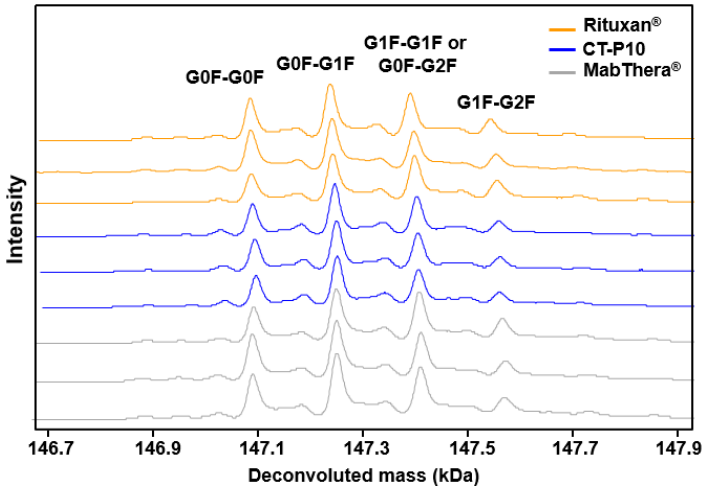


Figure 62: Deconvoluted Mass Spectra of Primary Structure for Representative Lots of CT-P10, Rituxan® and MabThera®

1.2 Higher Order Structure

Fourier Transform Infrared Spectroscopy (FTIR)

The secondary structure of samples was evaluated by comparison of the location and shape of the amide I and amide II bands, and of three bands (A, B and C) between 1,200 and 1,800 cm^{-1} in FTIR spectra (Figure 63).

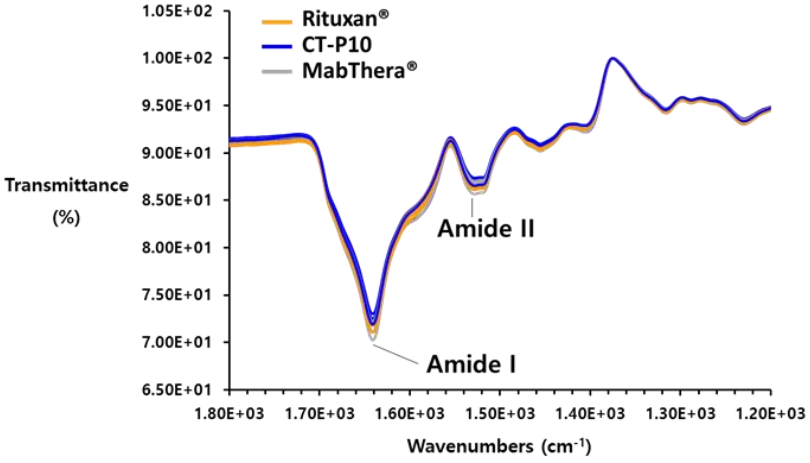


Figure 63: FTIR Difference Spectra of Higher Order Structure for Representative Lots of CT-P10, Rituxan® and MabThera®

Differential Scanning Calorimetry (DSC)

The thermal stability was evaluated by measuring the Tm. The thermograms were obtained with a scan rate of 1°C/min. The buffer subtracted, normalized signal was analyzed by non 2-state, 3 transition model to obtain the melting points of the transitions. Overlaid DSC thermograms for CT-P10, Rituxan® and MabThera® are shown in Figure 14.

Circular Dichroism (CD)

CD spectroscopy was performed to compare protein secondary and tertiary structure. Cells of quartz glass and optical path lengths of 1.000 and 0.100 cm were used for near-UV and far-UV spectra, respectively. The formulation buffer was measured as a blank and subsequently subtracted. Noise reduction was applied to the baseline corrected protein spectra using the device software of the spectrometer. Conversion of the measured CD signals to mean residue molar ellipticities was also conducted with software. The results of representative lots are shown in Figure 64 and Figure 65.

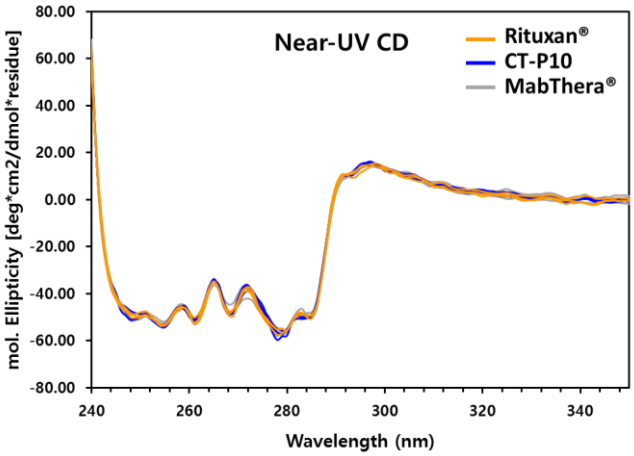


Figure 64: Near-UV CD Spectra of Higher Order Structure for Representative Lots of CT-P10, Rituxan® and MabThera®

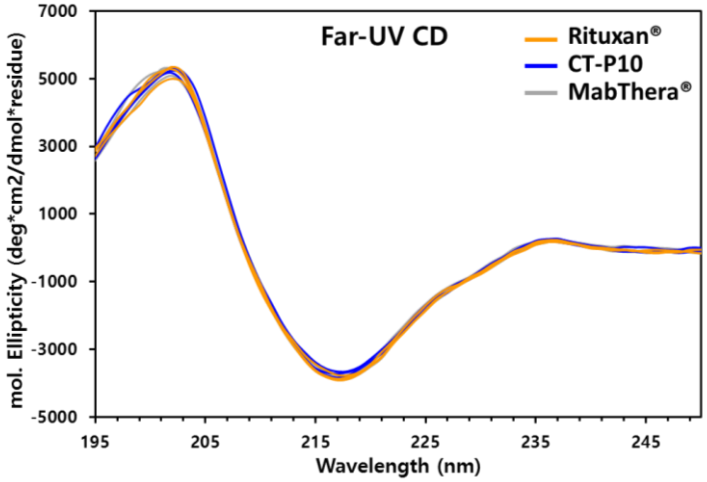


Figure 65: Far-UV CD Spectra of Higher Order Structure for Representative Lots of CT-P10, Rituxan® and MabThera®

Free Thiol Analysis

The free thiol groups (SH) in samples were measured using the 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) method (Ellman's assay). Cysteine standard and samples were mixed with DTNB, followed by measurement of absorbance at 412 nm. Free thiol groups were estimated in a sample by comparison to a standard curve composed of known concentrations of a sulfhydryl-containing compound such as cysteine. The results were reported as molar ratios (Free SH/IgG, μM/μM).

Disulfide Bonds

Samples were analyzed by comparing native and reduced peptide maps. For reduced peptide mapping analysis, the samples were reduced with Dithiothreitol (DTT), alkylated with Iodoacetamide (IAA) and for native peptide mapping analysis, no DTT was added to the sample. The samples were digested using trypsin after being desalted. The resulting peptides were separated by reversed-phase UPLC using a column with gradient of acetonitrile. An online mass spectrometer with an electrospray source was used to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis).

1.3 Protein Content

Protein Concentration (UV_{280})

Protein concentration was determined by absorbance at 280 nm (UV_{280}) and corrected with the absorbance at 320 and 350 nm.

Extractable Volume

The analytical procedure for extractable volume followed current USP <697>, previously included in USP <1> Injections. Only 7 lots of Rituxan® were available at the time of analysis.

1.4 Purity/Impurity Profile

SEC-HPLC

Size exclusion chromatography (SEC) was used to determine relative protein impurity (size variants) content and monomer content in samples. The samples were diluted with mobile phase buffer and the analysis was performed under non-denaturing conditions by HPLC on a column using aqueous buffered mobile phase. The isocratic elution profile was monitored using UV detection at 214 nm. The results of representative lots are shown in Figure 66.

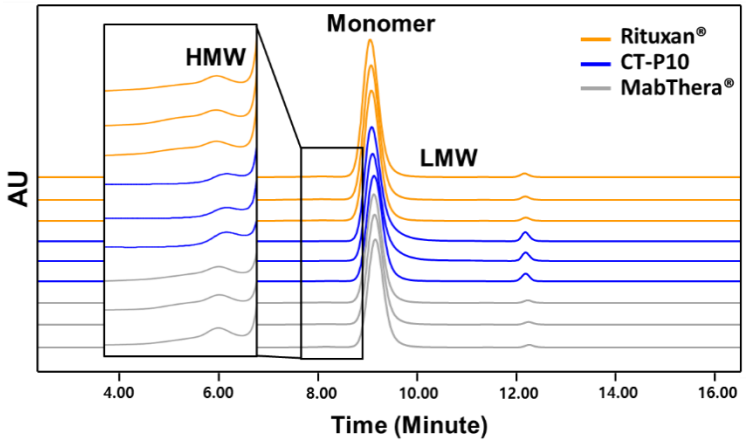


Figure 66: SEC-HPLC Chromatograms for Representative Lots of CT-P10, Rituxan® and MabThera®

SEC-MALS

Size exclusion chromatography with multi-angle laser light scattering (SEC-MALS) was performed to evaluate purity and provide molecular weight estimation of monomer and multimers present in samples. The assay was performed by HPLC using aqueous mobile phase buffer. The isocratic elution profile was monitored using MALS system. Molecular weight and monomer and dimer content were determined with MALS and RI detectors.

AUC

Sedimentation Velocity Analytical Ultra Centrifugation (SV-AUC) was undertaken at 20 °C and 45,000 rpm. Radial scans of the concentration profile were collected by absorbance at 280 nm, until full sedimentation was reached. The resulting data sets were analyzed using the program SEDFIT with a continuous c(s) distribution model, yielding best-fit distributions for the number of sedimenting species and the effective molecular weights. The resulting c(s)

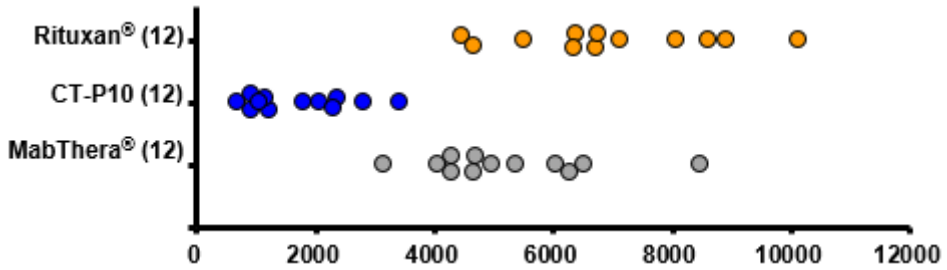
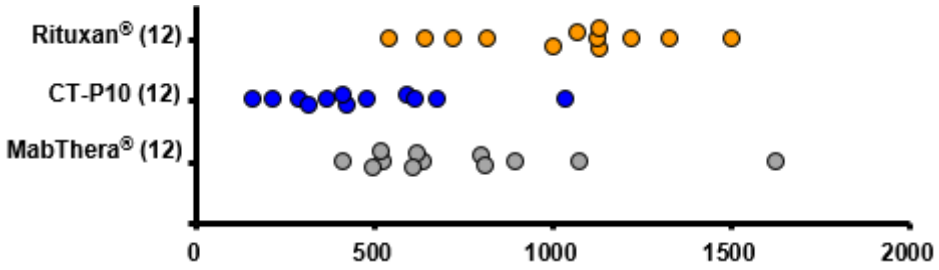
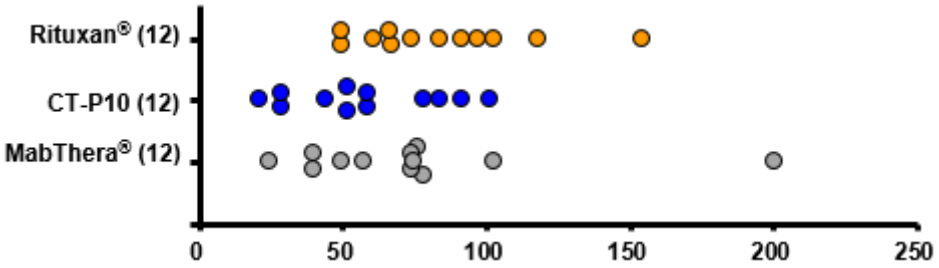
distribution profile was used to calculate the percentage of each species and the estimated molecular weights.

Non-reduced/Reduced CE-SDS

The capillary electrophoresis sodium dodecyl sulfate (CE-SDS) test method was used to determine purity/impurity levels in samples. For determination of purity, the corrected peak area % of sum of heavy chain and light chain, and NGHC, samples were reduced and subjected to electrophoresis under reducing conditions. For determination of the corrected peak area % of intact IgG and quantification of non-assembled IgG molecules, samples were alkylated and subjected to electrophoresis under non-reducing conditions.

MFI

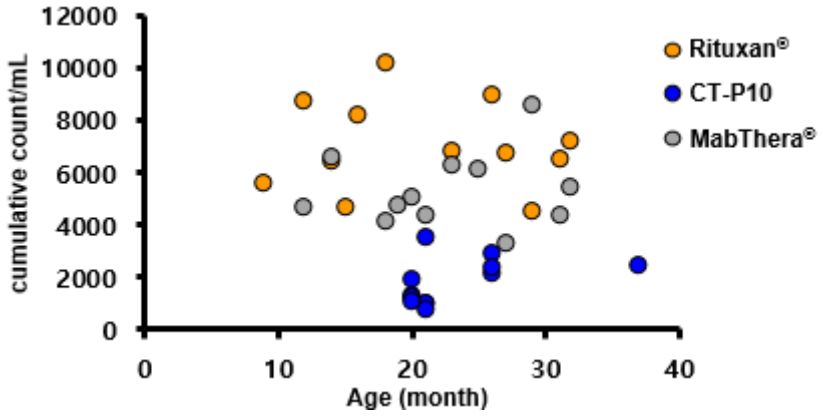
MFI detects sub-visible particles (SVP) by capturing images from the sample as it passes through the flow cell's sensing zone. An image was collected from each sample and was processed by the system software to extract each particle and its characteristics, including size, shape, transparency, and an individual image. An array of typical particle images from each sample and equivalent circular (or spherical) diameter were used for comparison. The MFI 5200 model used can detect SVP in the 1 µm to 100 µm size range. A total of 1 mL of undiluted sample was analyzed and the results were expressed as 'cumulative counts per mL'. The results of MFI analysis of CT-P10, Rituxan® and MabThera® lots are shown in Figure 67. To ensure a conservative evaluation, analysis included lots of Rituxan® between 9 and 32 months of age, CT-P10 drug product lots between 20 and 37 months of age, and MabThera® lots between 12 and 32 months of age at the time of analysis.

Size Range	Number of Sub-visible Particles (Cumulative Counts/mL)
1≤, <100 (µm)	
2≤, <100 (µm)	
5≤, <100 (µm)	

Number of lots used in the similarity study is indicated in brackets.
Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 67: Number of SVP in Each Size Range by MFI Analysis of CT-P10, Rituxan® and MabThera® Lots

Scatter plots for sub-visible particles by lot age, shown in Figure 68, illustrate that there was no impact of lot age on the results of sub-visible particle analysis by MFI.

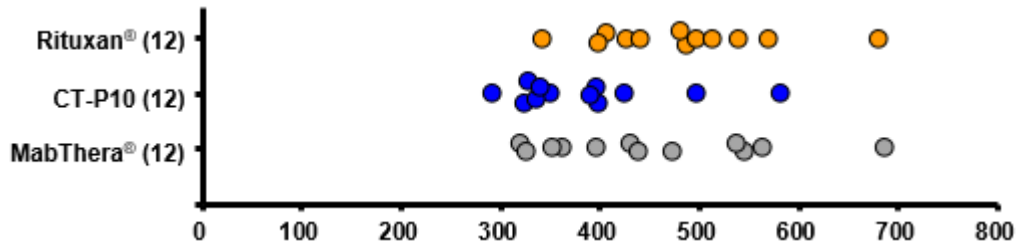
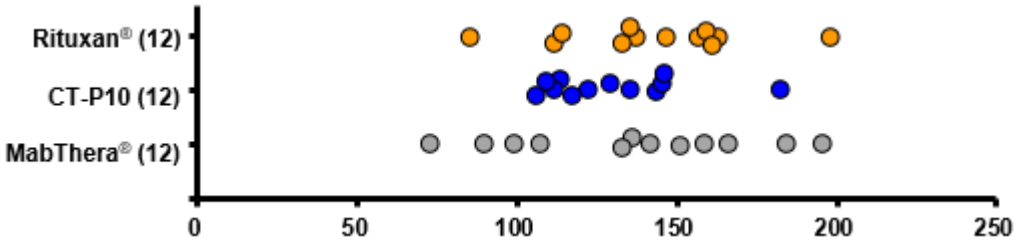
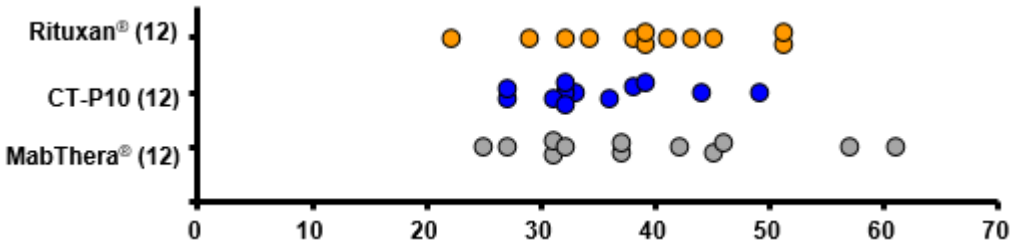
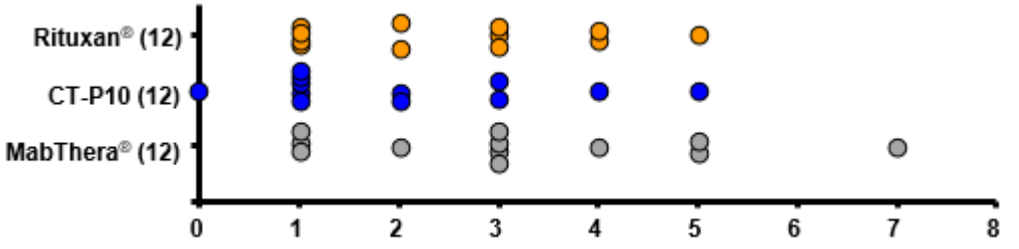


Some lots are overlapped with the same dots in CT-P10.
Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 68: Number of SVPs (1<, <100 µm) from MFI for CT-P10, Rituxan® and MabThera® Lots by Lot Age at the Time of Analysis.

Light Obscuration

The sub-visible particle content was determined using the light obscuration method described in Ph. Eur., current edition, General Chapter 2.9.19. *Particulate Contamination: Sub-visible Particles* (2016). The results of sub-visible particle analysis by light obscuration are shown in Figure 69.

Size Range	Number of Sub-visible Particles (Cumulative Counts/mL)
≥2 (µm)	
≥5 (µm)	
≥10 (µm)	
≥25 (µm)	

Number of lots used in similarity study is indicated in brackets.
Orange dots, blue dots and gray dots represent Rituxan® lots, CT-P10 lots and MabThera® lots, respectively.

Figure 69: Number of SVPs in Each Size Range by Light Obscuration Analysis of CT-P10, Rituxan® and MabThera® Lots

1.5 Charge Variants

IEF

IEF was used to determine the pI of charge variants in samples. Electrophoresis was performed on IsoGel agarose IEF plates in the range of pH 7 – 11 using a flatbed electrophoresis system. The samples were focused by running the gels. Following focusing, the gels were stained, dried and scanned. The pI values were calculated against pI markers (pI range: 10.65 – 6.90) using software and were compared to those of the reference standard.

IEC-HPLC

The IEC-HPLC method was used to evaluate the distribution of charge variants using cation exchange chromatography. The HPLC system was equipped with an analytical column and a guard column set at ambient temperature. Gradient elution was performed at a constant flow rate and UV signals were obtained at 214 nm. A total of 7 peaks were separated and detected by this method. Isoform peaks were integrated to provide relative % peak area.

1.6 Glycosylation

Oligosaccharide Profiling

The oligosaccharide profile test method was used to analyze the relative oligosaccharide content of G0F, G1F (both G1F isomers), G2F, Man5, G0 and G1 in samples used HPAEC-PAD after enzymatic (PNGase F) treatment. HPAEC-PAD separates carbohydrates via specific interactions between the hydroxyl groups of the oligosaccharide and the stationary phase of the column at high pH. The glycans move through the analytical column as anionic species and interact with the column based on glycan size, composition and linkage. HPAEC-PAD chromatograms of representative lots of Rituxan®, CT-P10 and MabThera® are shown in Figure 70.

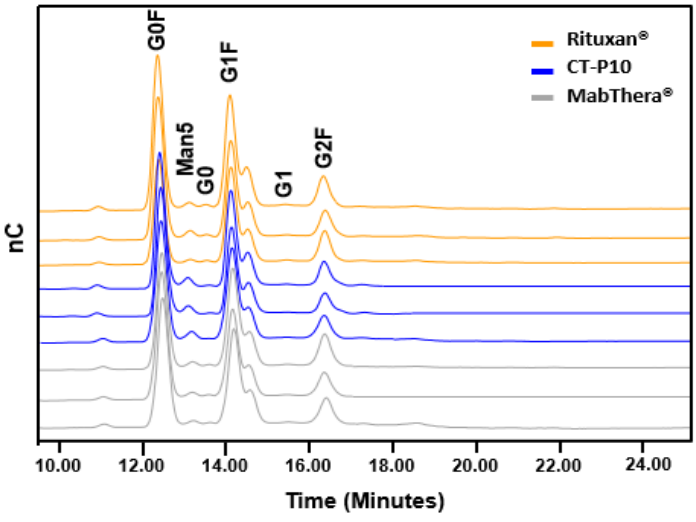


Figure 70: HPAEC-PAD Chromatograms for Representative Lots of Rituxan®, CT-P10 and MabThera®

N-linked Glycan Analysis

LC-MS analysis of the peptides generated during peptide mapping was used to identify all sites of glycosylation. Samples were prepared as described in the peptide mapping by LC-MS section using reduction, alkylation and tryptic digestion. Extracted ion chromatograms were used to quantify each oligosaccharide species. The percentage calculation was based on each glycosylation site. For each glycosylation site, all the detectable oligosaccharide structures were counted.

Sialic Acid Analysis

Sialic acids were released from the antibody by mild acid hydrolysis and separated by chromatography on a Waters HPLC system with fluorescent detector. The sialic acid content was quantified based on the response of sialic acid standards (NANA) relative to a standard. The results were reported as molar ratios (sialic acid/protein, mole/mole).

Monosaccharide Analysis

Monosaccharide analysis of the neutral and amino sugars was performed by hydrolyzing the samples followed by HPAEC-PAD analysis. Each monosaccharide was quantified relative to a monosaccharide standard. The results were reported as molar ratios (each monosaccharide/protein, mole/mole).

Glycation Analysis

Glycation levels were measured by reduced intact mass analysis (LC-ES-MS). Samples were treated to remove N-glycans, were reduced and were then subject to LC-ES-MS analysis. The m/z (mass/charge) data were collected and the mass spectra were deconvoluted. The percentage calculation was based on the deconvoluted spectra from both native and glycated forms of each chain.

Glycation sites were identified by LC/MS peptide mapping (Appendix 1.1) of digested samples. The identified glycation sites were evaluated for involvement in Fab and Fc functionality using the available crystal structures.

2. Biological Assays

The following section provides a brief description of the biological and functional assays used in 3-way analytic similarity studies and data from a subset of these test methods. All methods were appropriately validated or qualified and were determined to be suitable for their intended use. Representative dose-response curves are shown for the reference standard used in the assays.

Cell-based CD20 Binding (CELISA)

A CHO-K1 cell line expressing recombinant CD20 was used to determine CD20 binding. Cells were propagated, fixed and then blocked. Samples (from 0.24 ng/mL to 4,000 ng/mL) were added to the fixed cells and after washing, HRP-conjugated detection antibody was added and detected using a chromogenic substrate at 450 nm / 650 nm. The EC_{50} (effective concentration yielding a 50 % response) was deduced from four-parameter curve fitting of the dose-response curves using software. The relative EC_{50} was determined in comparison to the *in-house* reference standard.

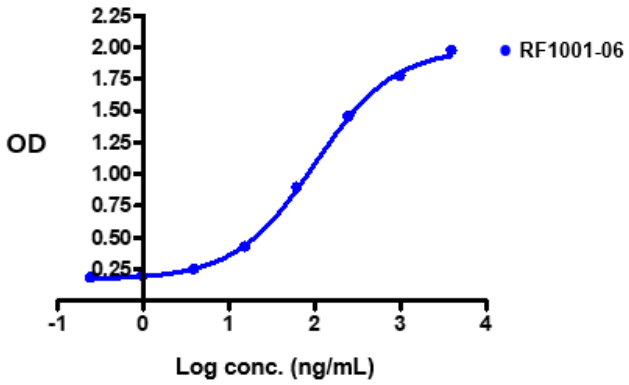


Figure 71: Representative Dose-Response Curve for Cell-based CD20 Binding

Apoptosis (FACS)

Apoptosis was measured using the Raji cell line (B lymphocyte) which expresses CD20 protein on the cell surface. A schematic illustration of the method is presented in Figure 72.

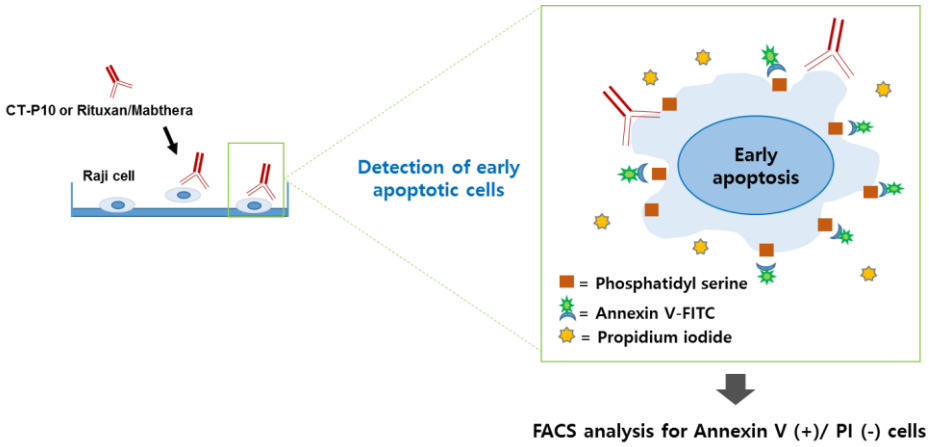


Figure 72: Illustration of Rituximab-mediated Apoptosis Assay

The relative apoptotic activity of samples was determined at three concentrations (0.13, 0.04 and 0.01 µg/mL) within the linear range of the apoptotic response as shown in Figure 73, and the results were compared with those of the *in-house* reference standard.

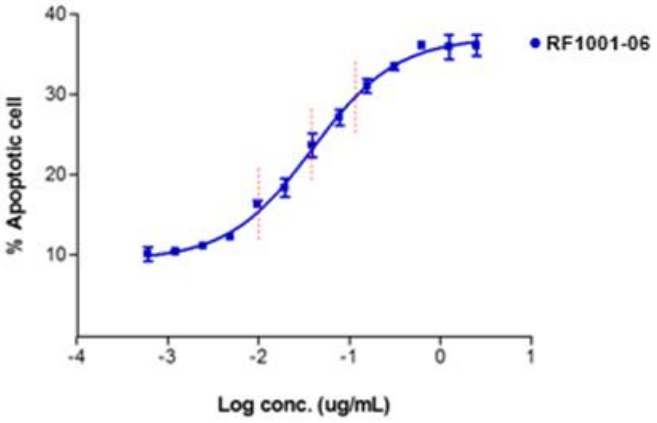


Figure 73: Representative Dose-Response Curve for Apoptosis Assay

C1q Binding

The C1q protein binds to the immunoglobulin CH2 domain and this interaction was detected using a sandwich ELISA. The ELISA signal is abrogated in the absence of C1q and enhanced at higher concentrations of IgG1 (in the presence of a constant saturating concentration of C1q).

Samples were immobilized onto a microplate and treated with C1q. Anti-C1q-HRP conjugate was added followed by a chromogenic substrate to measure the binding of samples to C1q at 450 nm / 650 nm. The optical density for reference standard and samples were fitted using a four-parameter curve fitting algorithm. The relative EC_{50} of samples was determined by comparison to the *in-house* reference standard.

Dose-dependent C1q binding at concentrations from 0.013717 to 30 µg/mL (3-fold dilution) was observed in the presence of *in-house* reference standard (RF1001-06) as shown in Figure 74.

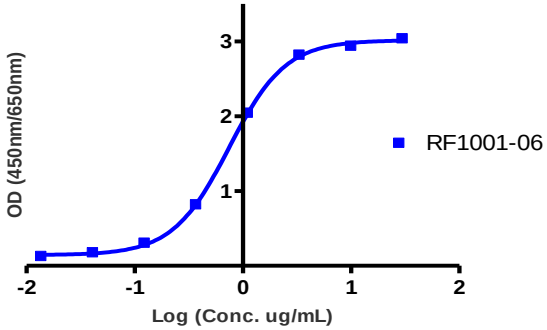


Figure 74: Representative Dose-Response Graph for C1q Binding (ELISA)

Fc Receptor Binding Affinity Using Surface Plasmon Resonance (SPR)

The Fc receptor was immobilized on the chip using an amine coupling reaction. Any unstable, immobilized Fc receptor was removed by washing. Serially diluted samples were used to generate binding curves and the binding affinity of samples was evaluated using software. The chips were regenerated using regeneration solution appropriate for the Fc receptor. Prior to the

next cycle of sample analysis, the re-use of immobilized chips was assessed based on the RU of the last sample run and that of the pre-run solution.

CDC

The cell-based anti-CD20 CDC assay was performed to measure CDC using normal human serum as a complement source and the Wil2-S cell line as target cell. WIL2-S cells were incubated with multiple concentrations of samples (from 0.008 µg/mL to 5 µg/mL) and diluted normal human serum for 2 hours. Cells were then incubated with CCK-8 solution to determine the metabolic activity of the cells.

WIL2-S metabolic activity was measured as an indicator of cell viability using a colorimetric method. The EC_{50} was determined by software using the 4-parameter logistic curve model and relative EC50 was obtained by comparison to the *in-house* reference standard. A schematic illustration of the method is presented in Figure 75.

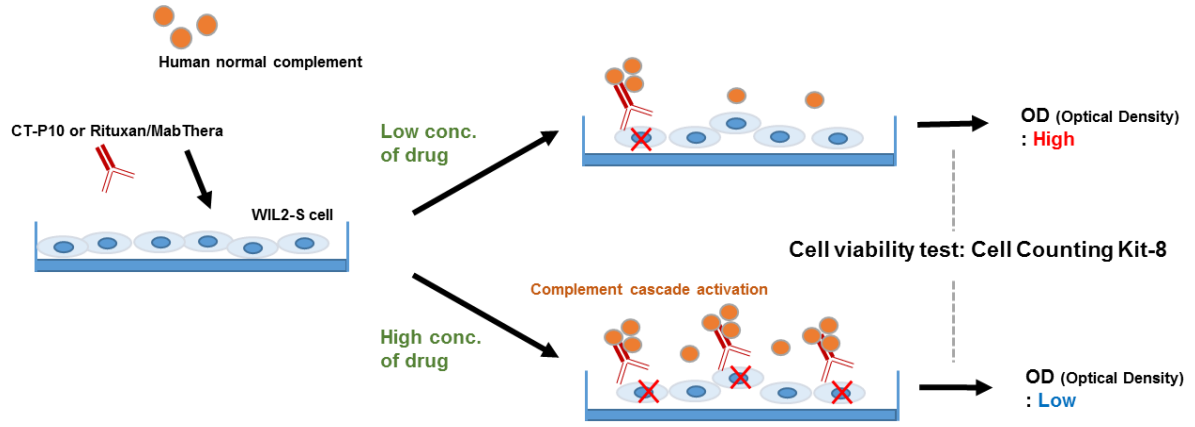


Figure 75: Schematic Illustration of CDC Assay

Dose-dependent CDC was observed in the presence of *in-house* reference standard (RF1001-06) concentrations of 0.008 µg/mL to 5 µg/mL (2.5-fold dilution) as shown in Figure 76.

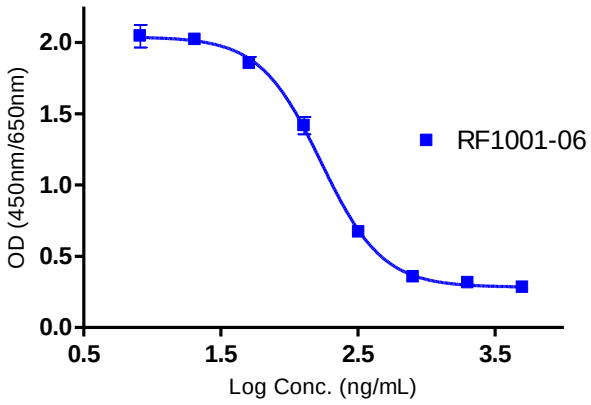


Figure 76: Representative Dose-Response Curve for CDC Assay

ADCC

ADCC using PBMCs

ADCC was measured as the antibody-dependent cell-mediated cytotoxicity mediated by effector cells through FcγR binding. The test was carried out using the Raji cell line (B lymphocyte) as target cell and human PBMCs of FcγRIIIa V/F allotype as effector cell. A schematic illustration of the method is presented in Figure 77.

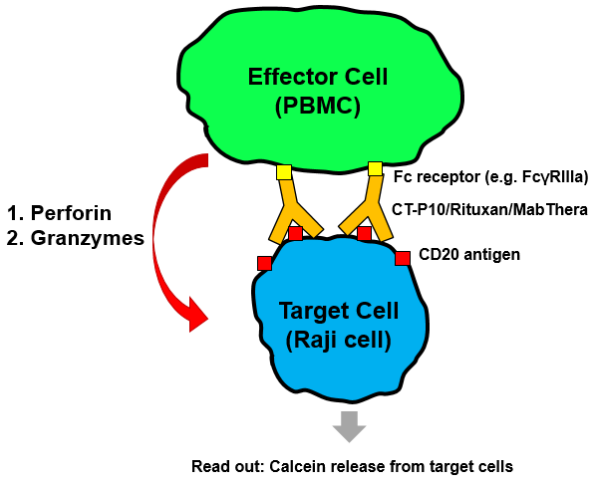


Figure 77: Illustration of Rituximab-mediated ADCC using PBMC against Raji Cells

The target cells were labelled with Calcein-AM and incubated with the samples at 3 concentrations (10.0, 35.0 and 122.4 ng/mL) within the linear range of the dose-dependent curve (from 0.2 ng/mL to 1,500 ng/mL) as shown in Figure 78. PBMC derived from a single healthy volunteer were added at an effector to target ratio of 16:1 and the mixture was incubated. The cytotoxicity was measured by calcein release, determined by fluorescence at 488 nm for excitation, 521 nm for emission and 515 nm for cut-off according to the formula below:

$$\text{Cell Cytotoxicity (\%)} = \frac{\text{Experimental Release} - \text{Spontaneous Release}}{\text{Maximal Release} - \text{Spontaneous Release}} * 100$$

The relative ADCC of CT-P10, Rituxan® and MabThera® samples were determined by comparison to the *in-house* reference standard.

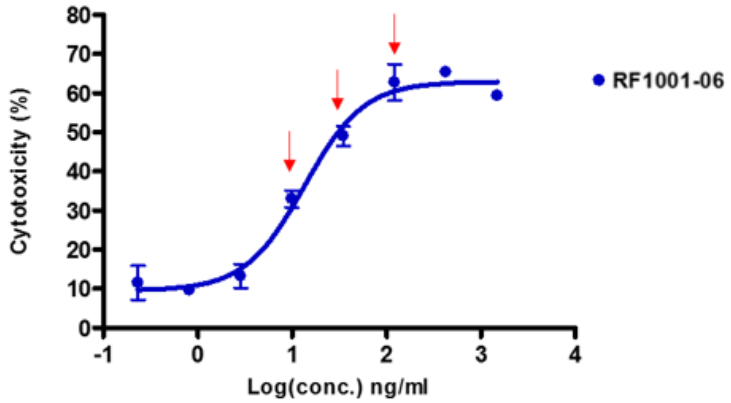


Figure 78: Representative Dose-Response Curve for ADCC Assay with Raji Target Cells and PBMC (FcγRIIIa-V/F) Effector Cells

ADCC using Reporter Assay

The ADCC reporter assay uses CD20 expressing Raji cells as target cells and a Jurkat engineered effector cell line expressing stably transfected NFAT-RE-Luciferase and FcγRIIIa-V158 as effector cells. Cross-linking of FcγRIIIa on the reporter cells by antibodies bound to target cells leads to activation of the NFAT response element and expression of luciferase. A schematic illustration of the method is presented in Figure 79.

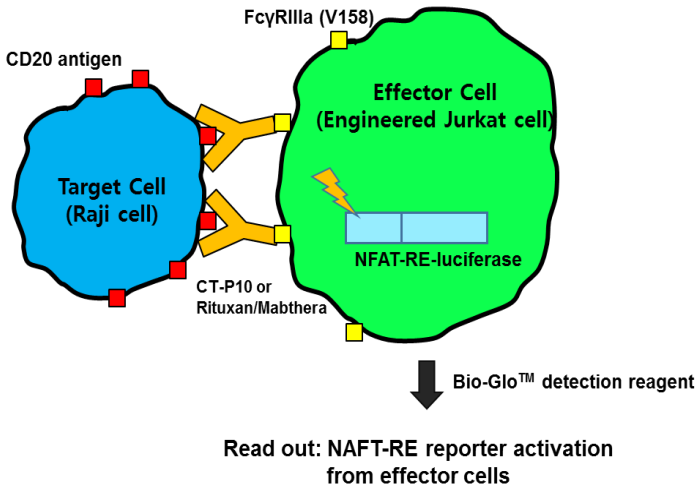


Figure 79: Illustration of Rituximab-mediated ADCC FcγRIIIa-V158 Reporter Assay

Raji cells were incubated with samples at concentrations from 0.01 ng/mL to 25,000 ng/mL. The effector cells, were incubated with antibody-bound target cells at an effector:target ratio of 2:1. The FcγRIIIa-specific activity was measured using a sensitive luciferase assay to detect luciferase expression driven by the NFAT response element.

The relative luminescence unit (RLU) values for the reference standard and samples were determined using 4-PL curve analysis. The relative cytotoxicity of samples was determined in comparison to the *in-house* reference standard.

Dose-dependent reporter ADCC was observed in the presence of *in house* reference standard (RF1001-06) concentrations of 0.01 ng/mL to 25,000 ng/mL (5.5-fold dilution) as shown in Figure 80.

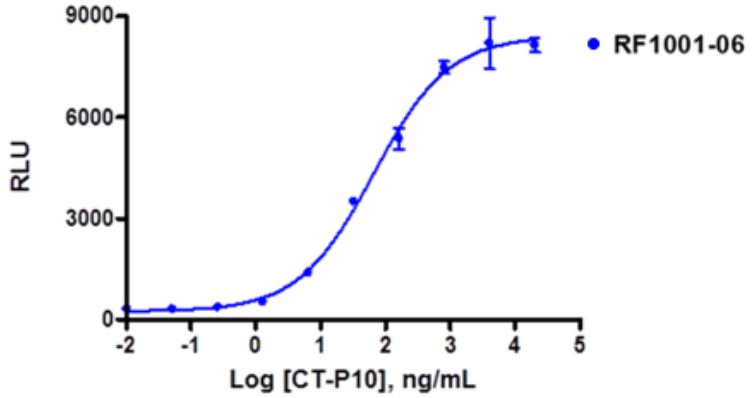


Figure 80: Representative Dose-response Curve for ADCC Reporter Assay (FcγRIIIa-V158)

ADCP

Primary monocyte-derived macrophages were used as effector cells and Raji cells were used as target cells.

Monocytes were isolated from human PBMCs using Pan Monocyte isolation kit and were cultured to enable differentiation into macrophages. Prior to incubation with antibodies, the target cells were labeled with PKH67, green fluorescence. The PKH67-stained Raji cells were incubated with samples. The macrophages differentiated from the purified monocytes were added and the phagocytosis was assessed by FACS analysis after staining macrophages with CD11b-APC, red fluorescence.

The % phagocytosis was calculated as the percentage of double-positive macrophages with respect to total target cells stained with PKH67.

A schematic diagram of the ADCP assay with cytometry plot is shown in Figure 81.

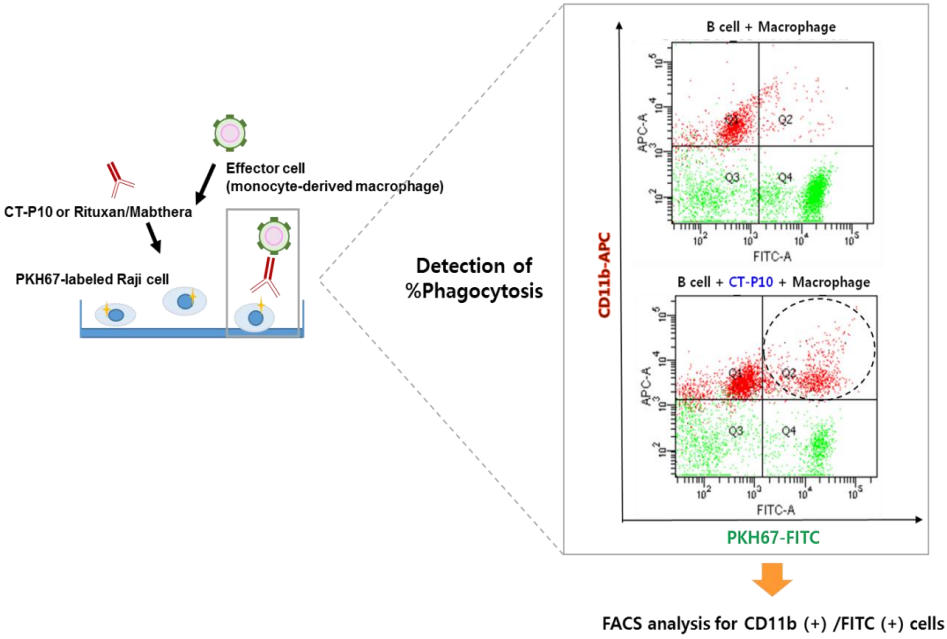


Figure 81: Illustration of CT-P10 Mediated ADCP

The relative phagocytosis was determined at 3 concentrations (1.56, 6.25 and 25.0 ng/mL) within the linear range of the ADCP dose-response curve (from 0.01 ng/mL to 1,600 ng/mL) as shown in Figure 82, and results were reported in comparison to the *in-house* reference standard.

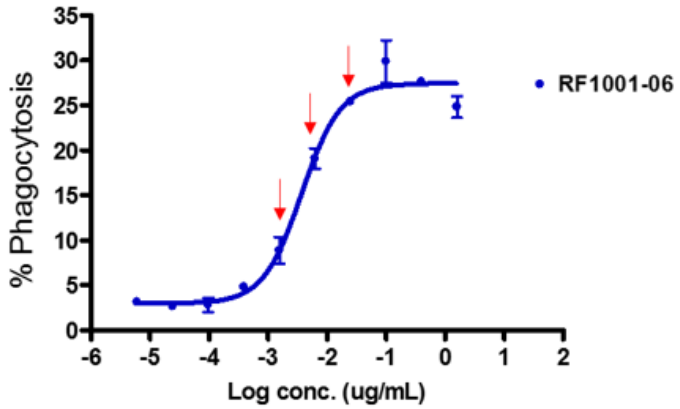


Figure 82: Representative Dose-response Curve for ADCP Assay

Appendix 2 Supportive Safety Results from CT-P10 FL Studies

Table 37: Additional SAE (Cut-off: February 23, 2018) in LTBFL Study (Study CT-P10 3.4) after 7-month Assessment

Preferred Term	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Gastritis	1 (0.8)	0
Cerebral infarction	1 (0.8)	0
Nasal neoplasm benign	0	1 (0.8)
Pneumonia	0	1 (0.8)
Pancreatitis	0	1 (0.8)
Interstitial lung disease	0	1 (0.8)
Bacterial infection	0	1 (0.8)

Table 38: Additional SAE (Cut-off: February 23, 2018) in Advanced FL Study (Study CT-P10 3.3) after July 31, 2017

Preferred Term	Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients	
Leukemic infiltration hepatic	1 (1.6)	0
Herpes zoster	1 (1.6)	0
Invasive lobular breast carcinoma	1 (1.6)	0

Table 39: AEs Leading to Permanent Study Drug Discontinuation in LTBFL Study (Study CT-P10 3.4)

Preferred Term (Severity, Intensity, Outcome)	CT-P10 (N=130)	Rituxan® (N=128)
	Number (%) of Patients	
Dermatitis (non-serious, grade 2, recovered/resolved)	1 (0.8)	0
Myocardial infarction (serious, grade 5, fatal)	1 (0.8)	0
Respiratory failure (serious, grade 5, fatal)	1 (0.8)	0
Squamous cell carcinoma of lung (serious, grade 3, recovered/resolved)	1 (0.8)	0

Table 40: AEs Leading to Permanent Study Drug Discontinuation in Advanced FL Study (Study CT-P10 3.3)

Preferred Term (Severity, Intensity, Outcome)	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Adenocarcinoma gastric (serious, grade 5, fatal)	1 (1.4)	0	0	0	1 (1.6)	0
Hypertension (serious, grade 3, recovered/resolved)	1 (1.4)	0	1 (1.4)	0	0	0
Infusion related reaction (non-serious, grade 2, recovered/resolved)	1 (1.4)	0	1 (1.4)	0	0	0
Liver function test abnormal (serious, grade 3, recovered/resolved)	1 (1.4)	0	1 (1.4)	0	0	0
Post procedural fistula (serious, grade 2, recovered/resolved)	1 (1.4)	0	1 (1.4)	0	0	0

Preferred Term (Severity, Intensity, Outcome)	Overall (Induction + Maintenance)		Induction Period		Ongoing Monotherapy Maintenance Period	
	CT-P10 (N=70)	Rituxan® (N=70)	CT-P10 + CVP (N=70)	Rituxan® + CVP (N=70)	CT-P10 (N=62)	Rituxan® (N=60)
	Number (%) of Patients					
Prostate cancer metastatic (serious, grade 3, not recovered/not resolved)	1 (1.4)	0	0	0	1 (1.6)	0
Tumor lysis syndrome (serious, grade 5, fatal)	1 (1.4)	0	1 (1.4)	0	0	0
Febrile neutropenia (serious, grade 3, recovered/resolved)	0	1 (1.4)	0	0	0	1 (1.7)
Hepatitis B (non-serious, grade 2, not recovered/not resolved)	0	1 (1.4)	0	0	0	1 (1.7)
Myeloproliferative disorder (non-serious, grade 1, not recovered/not resolved)	0	1 (1.4)	0	0	0	1 (1.7)
Lower respiratory tract infection (serious, grade 5, fatal)	0	1 (1.4)	0	0	0	1 (1.7)
Tuberculosis (non-serious, grade 2, not recovered/not resolved)	0	1 (1.4)	0	1 (1.4)	0	0

Appendix 3 Narrative Summary for Deaths Due to Adverse Event

Patient 1

Study	LTBFL study (Study CT-P10 3.4)
Indication	LTBFL since 13 Apr 2017
Event (PT)	Myocardial infarction
Age/ Sex/ Race	76/ M/ Asian
Cause of Death (Death Date)	Myocardial infarction ((b) (6))
Treatment	CT-P10 Number of doses received: CT-P10 (375 mg/m^2) 4 cycles (induction period)
Event Description	– Discovered dead at home – A post-mortem CT findings were suggestive of acute myocardial infarction
Other Clinical Data	– Comorbidities: asthma, dermatitis contact, hypertension, hyperuricemia, lipidosis, proteinuria and spinal column stenosis – Concomitant medications: amlodipine, allopurinol, atorvastatin, olmesartan, procaterol, budesonide, and formoterol

Patient 2

Study	LTBFL study (Study CT-P10 3.4)
Indication	LTBFL since 01 May 2017
Event (PT)	Respiratory failure
Age/ Sex/ Race	81/ F/ White
Cause of Death (Death Date)	Bronchilitis obliterans organizing pneumonia (BOOP) ((b) (6))
Treatment	CT-P10 Number of doses received: CT-P10 (375 mg/m^2) 4 cycles (induction period)
Event Description	– Experienced abdominal and flank pain – Transferred to an ICU secondary to severe hypoxia – "Do not resuscitate" was made, and autopsy was not performed
Other Clinical Data	– Comorbidities: coronary artery disease, gastroesophageal reflux disease, gout, hyperlipidemia, hypertension, hypothyroidism, interstitial lung disease, neuropathy peripheral, urinary tract infection, and seasonal allergy – Concomitant medications: ciprofloxacin, emla, ondansetron, acetylsalicylic acid, allopurinol, amlodipine, clopidogel, cetirizine, colestipol, gabapentin, lansoprazole, levothyroxine, metoprolol, ramipril, and budesonide w/formoterol

Patient 3

Study	LTBFL study (Study CT-P10 3.4)
Indication	LTBFL since 13 Oct 2013
Event (PT)	Pneumonia
Age/ Sex/ Race	66/ F/ White
Cause of Death (Death Date)	ARDS followed by multiorgan failure ((b) (6))
Treatment	Rituxan® Number of doses received: Rituxan® (375 mg/m^2) 8 cycles (maintenance period)
Event Description	– Pneumonia by influenza B virus – Developed ARDS followed by multiorgan failure and died – Autopsy not performed
Other Clinical Data	– Comorbidities: arthralgia, depression, dyspepsia, essential tremor, osteoporosis, peripheral sensory neuropathy, and pruritus – Concomitant medications: omeprazole, clomipramine, fluvoxamine, hydroxyzine, paracetamol, and propranolol, topiramate, ibandronate, bactrim, ultracet, and metoclopramide

Patient 4

Study	Advanced FL study (Study CT-P10 3.3)
Indication	Advanced FL (Ann Arbor stage IV) since 01 Jun 2015
Event (PT)	Tumor lysis syndrome (TLS)
Age/ Sex/ Race	74 / F/ White
Cause of Death (Death Date)	Cardiac and renal failure ((b) (6))
Treatment	CT-P10 Number of doses received: 1 cycle of CT-P10 (375 mg/m^2) plus CVP (induction period)
Event Description	– No TLS preventative measures during study drug infusion were given – TLS led to renal and cardiac failure. – Hyperkalemia, hypocalcemia, and hyperphosphatemia were absent
Other Clinical Data	– Comorbidities: coronary artery disease, cerebral arteriosclerosis, and hypertension – Concomitant medication: metoclopramide – Laboratory results: High level of baseline creatinine at screening, low level of glomerular filtration rate at baseline

Patient 5

Study	Advanced FL study (Study CT-P10 3.3)
Indication	Advanced FL (Ann Arbor Stage III) since 10 Jun 2014
Event (PT)	Adenocarcinoma gastric
Age/ Sex/ Race	71/ F/ White
Cause of Death (Death Date)	Deterioration of gastric adenocarcinoma ((b) (6))
Treatment	CT-P10 Number of doses received: 8 cycles of CT-P10 (375 mg/m^2) plus CVP and 6 cycles of CT-P10 (375 mg/m^2) (maintenance period)
Event Description	– Signet ring cell adenocarcinoma – Received chemotherapy (trastuzumab, cisplatin, and fluorouracil) for three weeks
Other Clinical Data	– Comorbidities: dislipidemia – Concomitant medication: omeprazole

Patient 6

Study	Advanced FL study (Study CT-P10 3.3)
Indication	Advanced FL (Ann Arbor stage IV) since 16 Jul 2015
Event (PT)	Leukemic infiltration hepatic
Age/ Sex/ Race	74/ M/ White
Cause of Death (Death Date)	Hepatic infiltration by carcinoma ((b) (6))
Treatment	CT-P10 Number of doses received: 8 cycles of CT-P10 (375 mg/m^2) plus CVP and 9 cycles of CT-P10 (375 mg/m^2) (maintenance period)
Event Description	– Symptoms of lower back and right hypochondrium pain, fever, asthenia, nausea, choluria, and jaundice – Progressed and died 9 days after symptoms developed
Other Clinical Data	– Comorbidities: hypothyroidism, type 1 diabetes mellitus, diastasis recti abdominis, constipation, hiatus hernia, and rhinitis – Concomitant medications: levothyroxine and glimepride, pantoprazole, olmesartan, and ciprofloxacin

Patient 7

Study	Advanced FL study (Study CT-P10 3.3)
Indication	Advanced FL (Ann Arbor stage IV) since 10 Mar 2015
Event (PT)	Respiratory tract infection
Age/ Sex/ Race	83/ M/ White
Cause of Death (Death Date)	Acute respiratory distress syndrome ((b) (6))
Treatment	Rituxan® Number of doses received: 8 cycles of Rituxan® (375 mg/m^2) plus CVP and 6 cycles of Rituxan® (375 mg/m^2) (maintenance period)
Event Description	– Fever and dyspnea developed – Autopsy was not performed, other information not available as the patient was treated in another clinic
Other Clinical Data	– Comorbidities: hypertension and chronic obstructive pulmonary disease – Concomitant medications: furosemide and combivent

Appendix 4 Full Inclusion and Exclusion Criteria

Study CT-P10 3.4

Inclusion Criteria

Each patient had to meet all of the following criteria to be enrolled in this study:

1. The patient was male or female aged ≥18 years.

2. The patient had histologically confirmed CD20+ FL Grade 1 to 3a according to the World Health Organization (WHO) 2008 classification (Jaffe, 2009); biopsy within 6 months before the first administration of the study drug.

3. The patient had at least 1 measurable tumor mass in 2 dimensions, and the mass had to be:

   - Nodal lesion >15 mm in the longest dimension, or
   - Nodal lesion >10 mm to ≤15 mm in the longest dimension and >10 mm in the shortest dimension, or
   - Extranodal lesion with both long and short dimensions ≥10 mm.

4. The patient had Ann Arbor stage II, III, or IV disease.

5. The patient had low tumor burden, based on the GELF criteria:

   - No B-symptoms
   - Lactate dehydrogenase less than the upper limit of normal (ULN)
   - Largest nodal or extra mass <7 cm
   - Less than 3 nodal sites with a diameter ≥3 cm
   - No significant serous effusions detectable clinically or by computed tomography (CT) (small, clinically non-evident effusions on CT scan were not deemed significant)
   - Spleen ≤16 cm by CT, and
   - No clinical organ failure or organ compression (e.g., ureteric obstruction)

6. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Oken *et al.*, 1982).

7. For both male and female patients and their partners of childbearing potential, the patient agreed to practice true abstinence (when this was in line with preferred and usual lifestyle of the patient) or to use 1 of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study drug (excluding women who were not of childbearing potential and men who have been sterilized):

   - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)

- Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
- Intrauterine devices

Male or female patients and their partners who had been surgically sterilized for less than 6 months prior to the first administration of the study drug must have agreed to use 1 medically acceptable method of contraception or practice true abstinence during study treatment.

Menopausal females must have experienced their last period more than 12 months prior to study entry (i.e., when the ICF was signed) to be classified as not of childbearing potential.

For both premenopausal women and women who were ≤12 months after the onset of menopause, the patient must have had a negative serum pregnancy test during the Screening Period.

8. Patient had adequate bone marrow, hepatic, and renal function reserve as evidenced by:

   - Hemoglobin level of ⩾10 g/dL
   - ANC of ⩾1500/mm^3
   - Platelet count of ⩾100 000/mm^3
   - Total bilirubin level of ≤2.0 mg/dL
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤3 × the ULN for the reference laboratory (≤5 × ULN for the reference laboratory with known hepatic involvement by lymphoma)
   - A serum creatinine level of ≤1.5 × ULN for the reference laboratory, or a calculated creatinine clearance by the Cockcroft-Gault equation (Rostoker *et al.*, 2007) of ⩾ 50 mL/min

9. The patient was able to understand verbal and/or written instructions and comply with all study requirements.

10. The patient was informed, given ample time and opportunity to read and/or understand about participation in the study, and had signed and dated the written ICF.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. The patient had received rituximab (or a rituximab proposed biosimilar product).

2. The patient had allergies or hypersensitivity to contrast agents for radiograph, murine, chimeric, human, or humanized proteins.

3. The patient had evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.

4. The patient had known central nervous system involvement or any evidence of spinal cord compression by lymphoma.

5. The patient had received previous treatment for NHL:

   - Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy)
   - All doses of corticoid therapy for treatment of NHL
   - Corticoid therapy within 4 weeks before the first administration of the study drug, with prednisone >20 mg/day (or equivalent doses of other steroid medications) for any purpose except NHL

6. The patient had a severe infection, such as sepsis, abscesses, active tuberculosis (TB), or opportunistic infections.

7. The patient had a known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (carriers of hepatitis B and hepatitis C were not permitted to enroll into the study).

8. The patient had New York Heart Association (Raphael *et al.*, 2007) Class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the previous 6 months before the first administration of the study drug.

9. The patient had any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before the first administration of the study drug.

10. The patient had a current or recent treatment (within 42 days before the first administration of the study drug or 5 times the half-life, whichever was longer, prior to screening) with any other investigational medicinal product or device.

11. The patient had uncontrolled diabetes mellitus, even after insulin treatment.

12. The patient was pregnant or lactating. Patients who were planning to be pregnant or to breastfeed before, during, or within 12 months after the last administration of the study drug were not permitted to enroll into the study.

13. The patient was taking a live, live-attenuated, or nonlive vaccine within 4 weeks before the first administration of the study drug.

14. The patient had evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, unstable pulmonary condition, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, or patient was high risk for treatment complications at the investigator's discretion.

Study CT-P10 3.3

Inclusion Criteria

Each patient had to meet all of the following criteria to be enrolled in this study:

1. Patient was male or female 18 years or older.

2. Patient had histologically confirmed FL according to the World Health Organization 2008 classification (Jaffe, 2009); grades 1 to 3a based on local laboratory review.

3. Patient had at least 1 measurable tumor mass that had not previously been irradiated, 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
   - extranodal lesion with both long and short dimensions ≥10 mm

4. Patient had confirmed CD20+ lymphoma, as assessed by local laboratory review.

5. Patient had Ann Arbor stage III or IV disease.

6. Patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Oken *et al*., 1982).

7. For both male and female patients and their partners of childbearing potential, patient agreed to practice total abstinence or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study treatment (excluding women who were not of childbearing potential and men who were sterilized):

   - Barrier contraceptives (male condom, female condom or diaphragm with a spermicidal gel)
   - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
   - Intrauterine devices

   Male or female patients and their partners who had been surgically sterilized for less than 6 months before study entry were to use 1 medically acceptable method of contraception or practice total abstinence.

   Menopausal females were to have experienced their last period more than 12 months before study entry (i.e., when the ICF was signed) to be classified as not of childbearing potential.

8. For both premenopausal women and women who were less than or equal to 12 months after the onset of menopause, patient had a negative serum pregnancy test during the Screening Period.

9. Patient had adequate bone marrow, hepatic, and renal function reserve as evidenced by:

    - Hemoglobin level of ≥8 g/dL
    - ANC of ≥1500/mm^3
    - Platelet count of ≥75000/mm^3
    - Total bilirubin level of ≤2.0 mg/dL
    - Aspartate aminotransferase and alanine aminotransferase levels of ≤3 × the upper limit of normal (ULN) for the reference laboratory (≤5 × ULN for the reference laboratory with known hepatic involvement by lymphoma)
    - A serum creatinine level of ≤1.5 × ULN for the reference laboratory, or a calculated creatinine clearance by the Cockcroft-Gault equation (Rostoker *et al.*, 2007) of ≥50 mL/min

10. Patient was able to understand verbal and/or written instructions and to comply with all study requirements.

11. Patient was informed, given ample time and opportunity to read and/or understand about participation in the study, and had signed and dated the written ICF.

Exclusion Criteria

A patient meeting any of the following criteria was excluded from the study:

1. Patient had received rituximab (or a rituximab proposed biosimilar product), cyclophosphamide, or vincristine.

2. Patient had allergies or hypersensitivity to murine, chimeric, human or humanized proteins, cyclophosphamide, vincristine, or prednisone.

3. Patient had evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.

4. Patient had known central nervous system involvement.

5. Patient had received previous treatment for NHL:

    - Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy). However, patients who had received radiotherapy as part of the palliative therapy were eligible if the last fraction of radiotherapy was administered at least 4 weeks prior to Day 1 of Cycle 1 and patients had recovered from all radiotherapy-related toxicities prior to randomization.
    - All doses of glucocorticoid therapy for treatment of NHL
    - Glucocorticoid therapy during the previous 4 weeks from Day 1 of Cycle 1, with prednisone >20 mg per day for any purpose

6. Patient had current diagnosis of active tuberculosis (TB) (defined by chest x-ray, computed tomography [CT], or proper image) or other severe infections, such as sepsis, abscesses, or opportunistic infections.

7. Patient had a known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. (Carriers of hepatitis B were not permitted to enroll into the study.)

8. Patient had New York Heart Association (Raphael *et al*., 2007) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 6 months before Day 1 of Cycle 1.

9. Patient had any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before Day 1 of Cycle 1.

10. Patient had current or recent (within 30 days before Day 1 of Cycle 1) treatment with any other investigational medicinal product or device.

11. Patient had uncontrolled diabetes mellitus, even after insulin treatment.

12. Patient was pregnant or lactating. Patients who were planning to be pregnant or to breastfeed before, during, or within 12 months after the last infusion of study treatment were not permitted to enroll into the study.

13. Patient was taking a live, live-attenuated, or nonlive vaccine within 4 weeks before Day 1 of Cycle 1 of study treatment.

14. Patient had evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational product, or patient was a high risk for treatment complications.