FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

October 10, 2018

BLA 761088
CT-P10, a proposed biosimilar to US-Rituxan (rituximab)
Applicant: Celltrion, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for CT-P10, a proposed biosimilar to Rituxan with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Table of Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse events
AUC	area under the curve
BLA	biologic license application
BPCI	Biologics Price Competition and Innovation
CDC	complement-dependent cytotoxicity
CR	complete response
CRu	complete response unconfirmed
C_{max}	maximum concentration
C_{trough}	trough concentration
CVP	cyclophosphamide, vincristine, prednisolone
DHP	Division of Hematology Products
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
ERK	extracellular signal-regulated kinase
DLBCL	diffuse large B-cell lymphoma
FC	fludarabine and cyclophosphamide
FDA	Food and Drug Administration
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GMR	geometric mean ratios
HR	hazard ratio
IV	intravenous
IWG	International Working Group
LC-MS	liquid chromatography coupled with mass spectrometry
LDH	lactate dehydrogenase
mg	milligrams
mL	milliliters
NHL	Non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PK	pharmacokinetic
PR	partial response
PFS	progression free survival
Q3w	every 3 weeks
RA	Rheumatoid Arthritis
SAE	serious adverse events
SD	stable disease
SPR	surface plasmon resonance
ULN	upper limit of normal
U/mL	units per milliliter

1. Introduction

Celltrion, Inc. (Applicant) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P10[1], a proposed biosimilar to US-licensed Rituxan (rituximab) (BLA #: 103705).

BLA 103705 for Rituxan was initially approved by the FDA on November 26, 1997, and is currently approved for the following indications:

1. 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.
2. Chronic Lymphocytic Leukemia (CLL)
   - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
3. Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.
4. Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids.
5. Moderate to severe Pemphigus Vulgaris (PV) in adult patients.

The Applicant is seeking licensure of CT-P10 for the following proposed indications:

1. 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.

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1 In this document, FDA generally refers to the Applicant's proposed product by the Applicant descriptor "CT-P10." FDA has not yet designated a nonproprietary name for the Applicant's proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products).

- 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.

This application was initially submitted on April 28, 2017. A Complete Response letter was issued February 28, 2018. A Complete Response was issued for clinical, product quality, and facility deficiencies. From a DHP clinical and statistical perspective, there were concerns that the safety and efficacy results of clinical study CT-P10 3.3 may not have provided support of a demonstration of no clinically meaningful differences between CT-P10 and the reference product, US-licensed Rituxan (also referred to as US-Rituxan), for the targeted oncology population.

The current BLA submission was submitted on May 28, 2018.

The purpose of the Oncologic Drugs Advisory Committee meeting is to discuss whether the totality of evidence present support licensure of CT-P10 as a biosimilar to US-Rituxan. This biosimilarity determination requires the following criteria, to be met:

1. CT-P10 is highly similar to US-Rituxan, notwithstanding minor differences in clinically inactive components, and
2. There are no clinically meaningful differences between CT-P10 and US-Rituxan in terms of the safety, purity, and potency of the product.

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the Public Health Service (PHS) Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

Section 351(k) of the PHS 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." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The 'totality of the evidence' submitted by an applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

Draft Points to Consider:

1. Discussion Point 1: Please discuss whether the evidence supports a demonstration that CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components.
2. Discussion Point 2: Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan.
3. Discussion Point 3: Please discuss whether there is adequate justification to support licensure for the proposed indications sought by the Applicant.

Voting Point 1:

Does the totality of the evidence support licensure of CT-P10 as a biosimilar product to US-licensed Rituxan for the following indications for which US-licensed Rituxan is currently licensed and for which the Applicant is seeking licensure?

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.

3. Chemistry, Manufacturing, and Controls (CMC)

Executive Summary

CT-P10 is a proposed biosimilar to US-licensed Rituxan. The Applicant used an array of analytical methods to assess the primary, secondary and higher order structure, physicochemical properties, and biological functions of CT-P10 in comparison to US-licensed Rituxan and EU-approved MabThera. Comparative data and analyses between CT-P10 and EU-approved MabThera are included in this briefing document for completeness, but were not necessary for FDA to make a conclusion about whether the submitted data support that CT-P10 is highly similar to US-licensed Rituxan.

For each attribute, pair-wise comparisons were conducted between US-licensed Rituxan, EU-approved MabThera, and CT-P10. Although minor differences in size variant profile, charge variant profile, deamidation and glycosylation profile were observed, additional data and justifications support that these differences do not preclude a finding that CT-P10 is highly similar to US-licensed Rituxan. The data establish analytical similarity between CT-P10 and US-licensed Rituxan and support that CT-P10 is highly similar to US-licensed Rituxan.

Pathophysiologic Role of CD20 and Mechanism of Action of Rituximab

CD20 is a non-glycosylated transmembrane phosphoprotein expressed on the surface of B cells during different stages of B cell development. CD20 expression begins at the pre-B cell stage and is sustained through the memory B cell stage. It is not expressed at the initial and end stage of B cell development, such as pro-B cells or terminally differentiated plasma cells [1]. CD20 is expressed on normal and malignant B cells, such as B cell lymphomas and lymphocytic leukemia [2, 3].

CD20 has no known natural ligand, and the exact biological function of CD20 is currently undetermined [1]. Studies have shown that CD20 may play a role in Ca^{2+} influx across the cell membrane [4]. However, CD20 knockout mice harbor no gross phenotype; have normal lifespans, reproductive success, and infection susceptibility; and largely normal B cell development (lower IgM expression and impaired CD19 induced intracellular Ca^{2+} response) [5]. US-licensed Rituxan is a chimeric murine/human IgG1κ monoclonal antibody directed against CD20. Rituximab binding to CD20 results in depletion of CD20-expressing B cells (normal or malignant). Clinical indications of US-licensed Rituxan include oncology diseases (such as NHL) and autoimmune diseases (such as RA). While the exact role of B cells in the pathophysiology of autoimmune disease is unclear [6], it is hypothesized that rituximab may suppress autoimmune disease by eliminating circulating B cells and suppressing autoantibody synthesis [7]. For the oncology indications, US-licensed Rituxan is effective in eliminating malignant B cells.

The molecular mechanism of action for US-licensed Rituxan is thought to be a combination of complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and apoptosis (Figure 1). CDC is a process in which antibody-coated target cells recruit and activate components of the complement cascade, leading to the formation of Membrane Attack Complex (MAC) on the cell surface and subsequent cell lysis. The process is initiated through binding of complement component 1q (C1q) to target-bound antibody [8]. Rituximab is highly efficient at mediating CDC of various B cell lines and fresh malignant B cell samples [9-12]. Studies conducted on animal tumor models suggest the anti-tumor activity of rituximab is dependent, at least in part, on complement activation [13, 14]. Furthermore, the role of rituximab in complement activation was confirmed in clinical observation [15]. Overall, the body of evidence strongly suggests that CDC is one of the major mechanisms of action for rituximab.

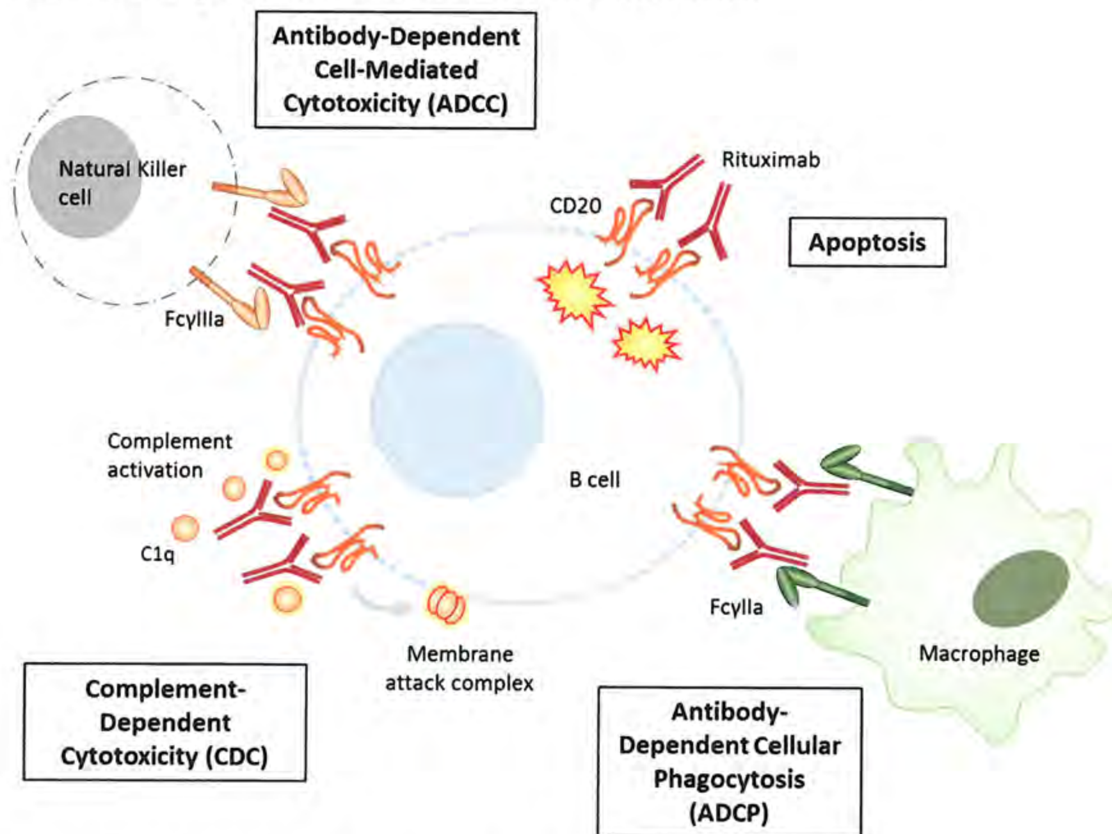
ADCC is a process in which antibody-coated target cells are lysed as a result of binding of the antibody Fc region to immune cells (effector cells). Rituximab binding to CD20-expressing cells leads to the recruitment of the effector cells (e.g., natural killer (NK) cells, neutrophils) that express Fc gamma receptor (FcγR) IIIa or other FcγRs. In vitro study shows that the binding of the antibody Fc region to the FcγRs on the effector cell triggers the release of cytokines and recruitment of more immune cells. These immune cells release proteases that effectively lyse the antibody-coated CD20-expressing cells, resulting in cell death [16]. In addition to the in vitro studies, clinical studies on FcγRIIIa polymorphism also suggest that ADCC is mechanistically involved in clinical response to rituximab. Follicular lymphoma patients with the FcγRIIIa 158 (VV) genotype (homozygous for valine) might have a better clinical response to rituximab than patients that have phenylalanine at that position (VF or FF) [17, 18], possibly due to higher affinity of VV FcγRIIIa than VF or FF FcγRIIIa for binding to IgG1 [19].

ADCP is a process in which antibody-coated target cells are phagocytized by macrophages, which express FcγRs on cell surface [20]. Upon rituximab binding to CD20-expressing cells, macrophages recognize the bound rituximab through FcγRs (e.g., FcγIIa), ultimately triggering phagocytosis. Such a mechanism has been demonstrated in several in vitro studies in which macrophage phagocytosis of malignant B cells were observed upon rituximab treatment [21-23].

In addition to effector mediated killing of CD-20 expressing B-cells, binding of rituximab to cell surface CD20 may also induce direct cellular apoptosis. It has been demonstrated that rituximab can induce cell death of malignant B cells in vitro in the absence of immune effector cells [24]. Certain antiapoptotic cellular pathways, such as p38 mitogen-activated protein kinase, nuclear factor-kappaB (NF-κB), extracellular signal-regulated kinase 1/2 (ERK 1/2), and protein kinase B (AKT) pathways, were inhibited in response to rituximab treatment [25]. One study showed a reduction in central nervous system lymphoma after rituximab injection directly into the cerebrospinal fluid, where limited immune responses are available, suggesting that this mechanism of apoptosis may play a role in human diseases [26].

CDC, ADCC, ADCP, and apoptosis all appear to be potential mechanisms of action for US-licensed Rituxan. It is uncertain which of the mechanisms of action play the predominant role in efficacy of the autoimmune and oncology diseases. Current data suggest it is plausible that different mechanisms are likely involved in different disease settings [27].

Figure 1. Proposed Mechanism of Action of Rituximab



Source: FDA illustration based on published literature.

CT-P10 Manufacturing

CT-P10 is produced using a mammalian cell line expanded in bioreactor cultures followed by a drug substance purification process that includes various steps designed to purify the protein product. Residual levels of process-related impurities (e.g., host cell proteins, host cell DNA, and those specific to CT-P10 manufacturing process) are evaluated and controlled as part of the CT-P10 drug substance in-process and release testing. The data provided by the Applicant demonstrate that the CT-P10 drug substance manufacturing process sufficiently reduces the impurity levels to those consistent with contemporary manufacturing expectations.

The CT-P10 drug product is produced in two strengths: a 100 mg/10 mL solution and a 500 mg/50 mL solution of CT-P10, both in single-use vials, which reflects the same strengths and presentations approved for US-licensed Rituxan. The formulation buffer (sodium chloride, sodium citrate, polysorbate 80, at pH 6.5) for CT-P10 contains the same excipients as US-licensed Rituxan and EU-approved MabThera.

The Applicant modified the manufacturing processes for CT-P10 drug substance and drug product during the course of product development. Comparability studies were performed to demonstrate product comparability for the pre- and post- change materials in each case. The CT-P10 drug product lots manufactured for clinical and intended commercial use were included in the analytical similarity assessment.

Analytical Similarity Assessment

The objective of the analytical similarity assessment is to support a demonstration that the proposed biosimilar product CT-P10 is "highly similar" to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components. The analytical similarity data package submitted to the FDA consisted of three pairwise comparisons: CT-P10 to US-licensed Rituxan, CT-P10 to EU-approved MabThera, and EU-approved MabThera to US-licensed Rituxan. Comparative data and analyses between CT-P10 and EU-approved MabThera are included in this briefing document for completeness, but were not necessary for FDA to make a conclusion about whether the submitted data support that CT-P10 is highly similar to US-licensed Rituxan.

FDA performed statistical analyses of the Applicant's submitted data. Fifteen lots each of CT-P10 drug product, US-licensed Rituxan, and EU-approved MabThera were used in the analytical similarity assessment, except for protein content (see Protein Content section). The expiration dates of the US-licensed Rituxan lots and EU-approved MabThera lots each spanned approximately three years (2016 to 2019) covering varying stages of the product shelf life. The CT-P10 lots that were analyzed were manufactured between 2013 and 2015.

CT-P10 drug product and US-licensed Rituxan are both produced in two strengths: 100 mg/10 mL and 500 mg/50 mL. The Applicant used only the 500 mg/50 mL strengths of CT-P10 drug product and US-licensed Rituxan in the similarity assessment and stated that there are no attributes, except extractable volume, expected to differ by strength/presentation. This is based

on the Applicant's assessment of the similarity between the CT-P10 manufacturing processes and comparability between the products and the quality attributes of the 100 mg/10 mL and 500 mg/50 mL presentations.

The Applicant selected a variety of methods to be used in the analytical similarity assessment (Table 1). These include orthogonal methods that measured the same quality attribute by differing means. The analytical methods were appropriately validated or qualified and are suitable for their intended use.

Table 1. Quality Attributes and Methods Used to Evaluate Analytical Similarity of CT-P10, US-licensed Rituxan, and EU-approved MabThera

Quality Attribute	Methods
Primary Structure	Amino acid analysis by peptide mapping using liquid chromatography coupled with mass spectrometry (LC-MS)
	Amino acid composition analysis
	Molar absorptivity and extinction coefficient calculation using UV280 absorption and results from amino acid composition analysis
	N- and C-terminal sequences by peptide mapping using LC-MS/MS
	Comparison of tryptic peptide map by visual inspection
	Molecular weight by intact mass as measured by LC-MS
Protein Content	Concentration by ultraviolet (UV) spectroscopy at 280 nm
Higher Order Structure	Fourier Transform Infrared Spectroscopy (FTIR)
	Differential Scanning Calorimetry (DSC)
	Circular Dichroism (CD)
	Free thiol analysis by Ellman's assay
	Disulfide bond analysis by native and reducing peptide mapping (LC-MS)
Size Variants/ Aggregates	Size exclusion chromatography (SEC-HPLC) with UV detection
	SEC with multi-angle laser light scattering (MALS)
	Sedimentation Velocity Analytical Ultra Centrifugation (SV-AUC)
	Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS, Reducing and Non-Reducing)
Charge Variants	Ion-exchange chromatography (IEC-HPLC)
	Isoelectric focusing (IEF)

Quality Attribute	Methods
Post-Translational Modification	Deamidation, Oxidation, N-terminal glutamine, and C-terminal Lysine as measured by peptide mapping
Glycosylation	N-linked glycan analysis by High-Performance Anion Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD)
	N-linked glycan analysis using LC-MS
	Sialic acid content analysis by HPLC with fluorescent detector
	Monosaccharide composition analysis by HPAEC-PAD
	Glycation analysis by reducing intact mass analysis (LC-ES-MS)
Biological activity	CDC activity assay (WIL2-S cells as target cells, and normal human serum as complement source)
	ADCC activity assay [Raji cells as target cells, and peripheral blood mononuclear cells (PBMC) as effector cells]
	ADCC reporter assay (Raji cells as target cells, and engineered Jurkat cells as effector cells with integrated reporter gene)
	ADCP activity assay (Raji cells as target cells, and primary monocytes-derived macrophages as effector cells)
	Cellular apoptosis assay using flow cytometry
	Cell-based CD20 binding assay by enzyme-linked immunosorbent assay (ELISA)
	C1q binding affinity by ELISA
	FcγRIIIa V type binding affinity by surface plasmon resonance (SPR)
	FcγRIIIa F type binding affinity by SPR
	FcγRIIIb binding affinity by SPR
	FcγRIIa binding affinity by SPR
	FcγRIIb binding affinity by SPR
	FcγRI binding affinity by SPR
	FcRn binding affinity by SPR

For comparative analytical testing, all test samples were performed in a side-by-side manner, except for SEC-HPLC, CE-SDS, IEF, IEC-HPLC, and oligosaccharide profiling. For these assays, CT-P10 drug product lot release data were used for the similarity assessment, and CT-P10 lots were tested within 1 month of manufacture.

Depending on the criticality of the attributes, the Applicant used three types of statistical approaches to evaluate the analytical data in support of a demonstration of biosimilarity: equivalence testing, quality range comparison, and visual comparison. Biological activity as measured by CDC and ADCC assays were evaluated using statistical equivalence testing with the equivalence margins (EM) of $\pm 1.5\sigma_R$, where σ_R represents the US-licensed Rituxan product variability and is estimated by the US-licensed Rituxan lot values generated by the Applicant. The Quality Range (QR) approach was used to evaluate product variants, impurities, N-glycosylation, and other related biological activities. The QRs were defined by the variability observed in US-licensed Rituxan. The Applicant defined the QRs as [mean ± 3SD] for most attributes (exceptions are noted below). Primary, secondary and tertiary structures, impurities (as measured by orthogonal methods), certain post-translational modifications, and low criticality biological activities were evaluated using the visual comparison approach.

Primary Structure

The Applicant designed the CT-P10 amino acid sequence to match that of US-licensed Rituxan. The expression construct for CT-P10 was sequenced to confirm that the expected nucleotide sequence was present to express the correct amino acid sequence. Further, the primary sequence of CT-P10 was analyzed using multiple methods to confirm that CT-P10 has the same amino acid sequence as US-licensed Rituxan.

As part of the analytical similarity assessment, the Applicant used several direct and indirect methods to determine the primary sequence of CT-P10, US-licensed Rituxan, and EU-approved MabThera. The peptide maps were generated from reduced samples independently treated with trypsin, Asp-N, and Lys-C to obtain full coverage. All samples were analyzed using RP-HPLC followed by MS for peptide identification. The detected peptides from the heavy and light chains of all three drug products matched the expected peptides from the amino acid sequence. The Applicant confirmed that the CT-P10 drug product amino acid sequences matches that of US-licensed Rituxan and EU-approved MabThera by MS/MS analysis.

The Applicant conducted amino acid composition analysis of the three products. Peptide bonds were hydrolyzed and amino acids were analyzed by RP-HPLC. Amino acid concentrations were calculated based on calibration to standard amino acid mixtures and expressed as molar ratios relative to leucine. Amino acid composition results are similar across the three drug products.

Intact Mass analysis for all product samples yielded 4 possible masses corresponding to the glycoforms G0F-G0F, G0F-G1F, G1F-G1F or G0F-G2F, and G1F-G2F. The observed masses closely match the expected masses, and the results are similar across the three drug products (Table 2).

Table 2. Intact Mass Results

Product	Intact Mass (mean, Da)			
	G0F-G0F	G0F-G1F	G1F-G1F or G0F-G2F	G1F-G2F
US-Rituxan	147,087.0	147,248.4	147,409.8	147,571.6
CT-P10	147,085.8	147,247.5	147,408.9	147,570.0
EU-MabThera	147,087.0	147,248.3	147,409.8	147,571.4

Source: Intact Mass mean derived from the Applicant's 351(k) submission.

Higher Order Structure

The folding of antibodies into their correct three-dimensional structures are important for biological functions and pharmacokinetics. Intra- and inter-chain disulfide bond positions for 16 disulfide bonds per molecule were confirmed in all three products. The levels of free thiol per mole product are similar among the three products. Secondary and tertiary structures were analyzed using FTIR, CD, and DSC. All three methods yielded overlapping spectra among the CT-P10, US-licensed Rituxan and EU-approved MabThera lots evaluated.

Protein Content

The Applicant evaluated protein concentration in the similarity assessment, as protein content impacts dosing and efficacy.

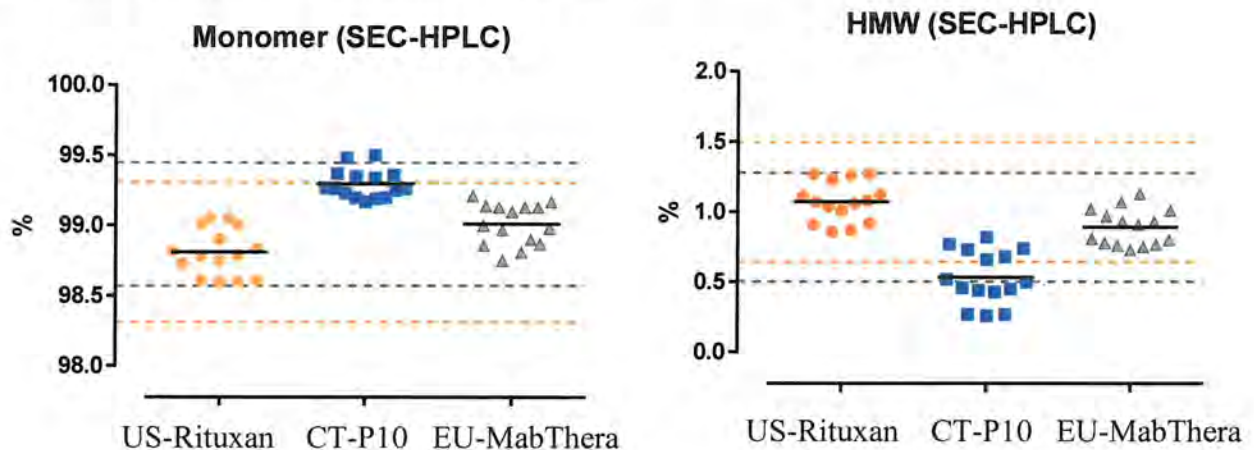
Protein concentration was read at UV 280nm and calculated using the extinction coefficient (b) (4) (b) (4) which was both theoretically and experimentally determined. Of the 15 CT-P10 drug product lots tested, 12 (80%) are within the QR (9.74 – 10.76 mg/mL) defined by the variability in protein concentration observed in US-licensed Rituxan. The concentrations of the three CT-P10 drug product lots that are outside of the QR were 9.7 mg/mL. During development of the CT-P10 drug product manufacturing process, the Applicant introduced a process adjustment to more closely match the protein concentration the Applicant measured for US-licensed Rituxan lots. Eleven of the 12 CT-P10 lots manufactured after this manufacturing adjustment fall within the US-licensed Rituxan QR for protein concentration.

Aggregates

Aggregates are important quality attributes of therapeutic proteins because they could impact product efficacy and immunogenicity [28, 29]. Biopharmaceuticals commonly contain low levels of protein aggregates at the time of release and through the storage. They are measured for lot release and as part of long-term stability studies and are controlled by release requirements and expiry periods. The monomeric and aggregate or high molecular weight (HMW) protein profiles were characterized by multiple orthogonal methods: SEC-HPLC, SEC-MALS, and SV-AUC.

The SEC-HPLC method was used to quantify monomer, HMW, and low molecular weight (LMW) species abundance. The SEC-HPLC results from the similarity assessment are summarized in Figure 2 for monomer and HMW species. LMW species were low in all three products (<0.5%). Although less than 90% of the CT-P10 lots are within US-licensed Rituxan QR for size purity as measured by SEC-HPLC, the overall difference in species is small and associated with lower risk because CT-P10 has fewer product-related size impurities than US-licensed Rituxan.

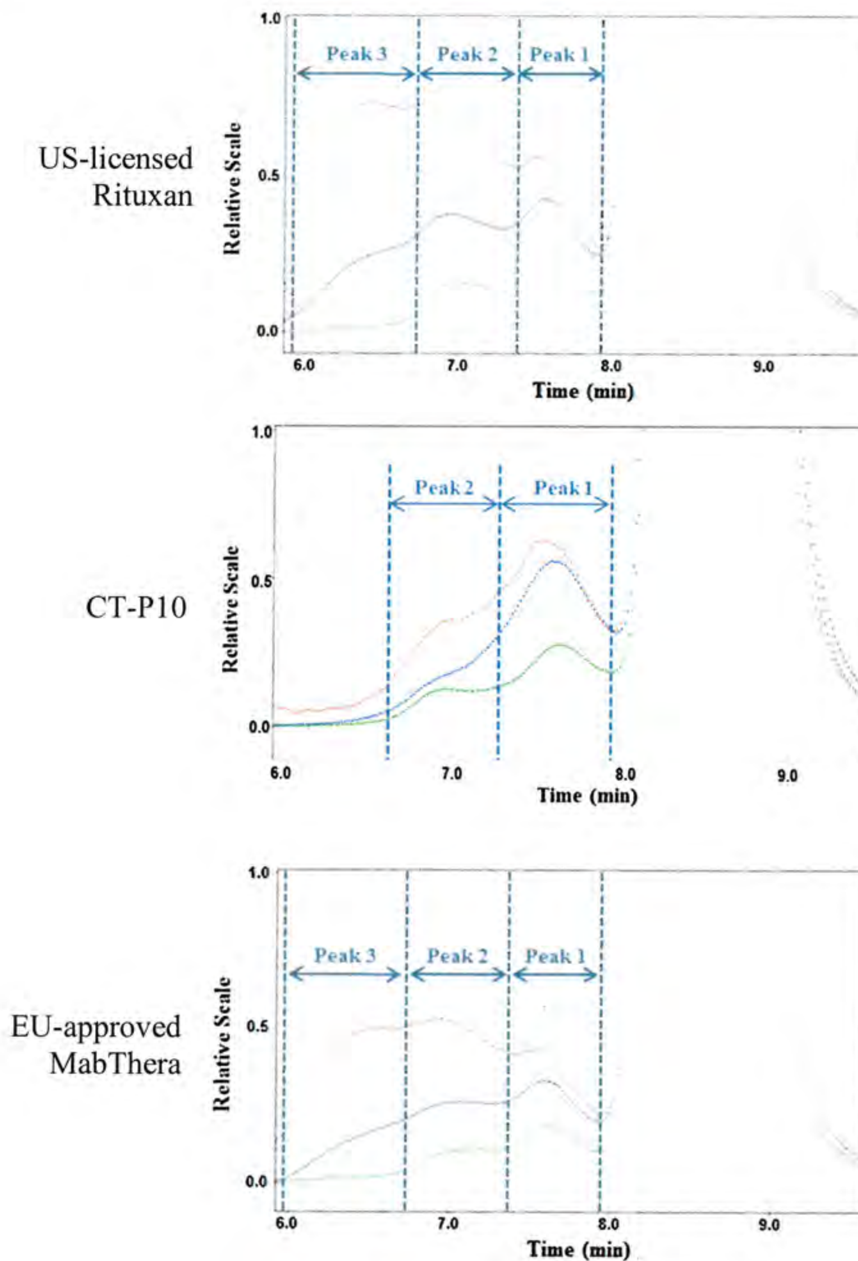
Figure 2. Comparison of % Monomer and % HMW Species in US-licensed Rituxan, CT-P10, and EU-approved MabThera by SEC-HPLC



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) submission.

SEC-MALS and SV-AUC data further characterize the abundance of monomeric and HMW species. Molecular weight, monomer and dimer content were determined with MALS and refractive index (RI) detectors. This method calculates monomer and HMW species abundance as measured by UV and MALS and it estimates the molecular weight of the species. Statistical analysis of the results shows that %monomer and %HMW of CT-P10 lots measured by SEC-MALS are all within the QRs of US-licensed Rituxan and EU-approved MabThera. The SEC-MALS data reveals that the average molecular weight of HMW forms for CT-P10 was 197 kDa, while those of US-licensed Rituxan and EU-approved MabThera were 303 kDa and 293 kDa. This is likely due to the difference in the size distribution of the HMW species (Figure 3.).

Figure 3. Size Distribution Analysis of HMW Species in US-licensed Rituxan, CT-P10, and EU-approved MabThera by SEC-MALS

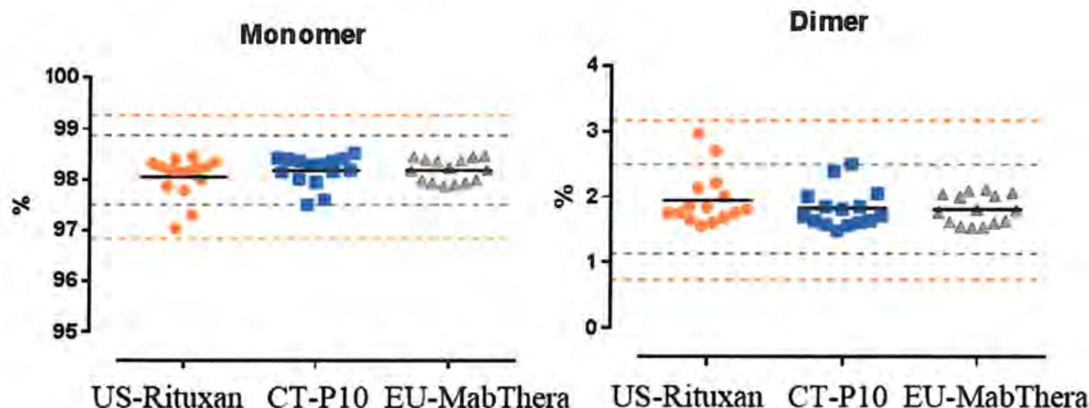


Peaks indicate different HMW forms; Detection: UV (green), RI (purple) and LS (red).
Source: Figure excerpted from the Applicant's 351(k) BLA submission.

In addition, the three drug products were analyzed by SV-AUC. A single dominant monomer species (97.04 – 98.52% in abundance) at approximately 6.03 – 6.32 S and a dimer species (1.48 – 2.96% in abundance) at approximately 8.60 – 9.19 S were observed in all lots. Statistical

analysis shows that %monomer and %dimer of CT-P10 lots measured by SV-AUC are within the QR of US-licensed Rituxan. The SV-AUC data for the three products are shown in Figure 4.

Figure 4. Percentage of Monomer and Dimer in US-licensed Rituxan, CT-P10, and EU-approved MabThera by SV-AUC



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) submission.

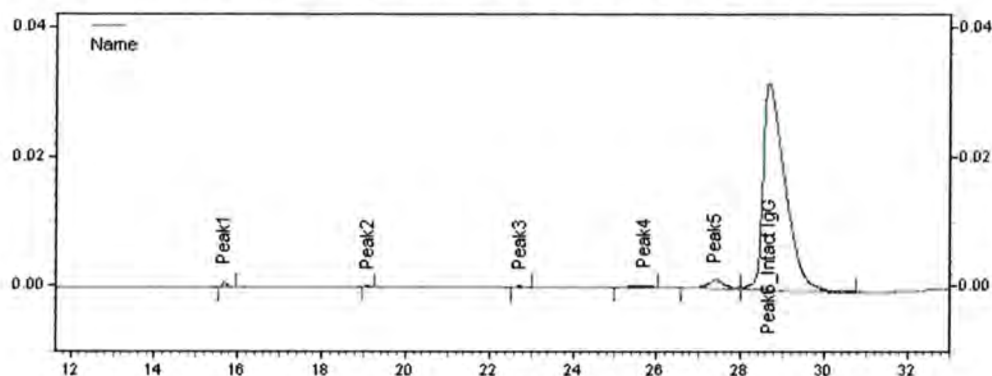
Overall, the levels of aggregates in CT-P10 lots, measured by three orthogonal methods, did not exceed the upper limit of the QR of the US-licensed Rituxan lots. A slight difference in the distribution of the HMW species molecular weight was observed by SEC-MALS; CT-P10 has less complex HMW species but in similar abundance compared to US-licensed Rituxan and EU-approved MabThera. Here, the aggregation levels observed and the identified differences do not preclude a demonstration that CT-P10 is highly similar to US-licensed Rituxan.

Size Variants

Product-related size variants, such as HMW and LMW species, can have the potential to affect product potency and immunogenicity. Assessment of HMW species were discussed in the aggregates section above. LMW species, such as "non-assembled forms" of heavy chain (HC) and light chain (LC), and aglycosylated forms were evaluated using non-reducing and reducing CE-SDS.

Non-assembled forms of HC and LC are detected as Peak 1 to Peak 5 in non-reducing CE-SDS chromatogram which represents L1, H1, L1H1, H2, H2L1, respectively (Figure 5.). The intact product (Intact IgG) is detected as the main peak in the electropherogram.

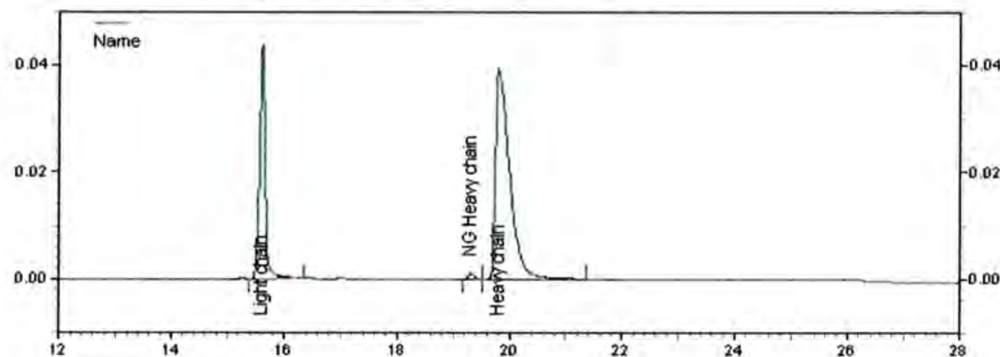
Figure 5. Non-reducing CE-SDS of CT-P10 Drug Product



Source: Figure excerpted from the Applicant's 351(k) BLA submission.

A representative reducing CE-SDS electropherogram of CT-P10 drug product is shown in Figure 6.. The three peaks represent LC, aglycosylated HC (NGHC), and HC.

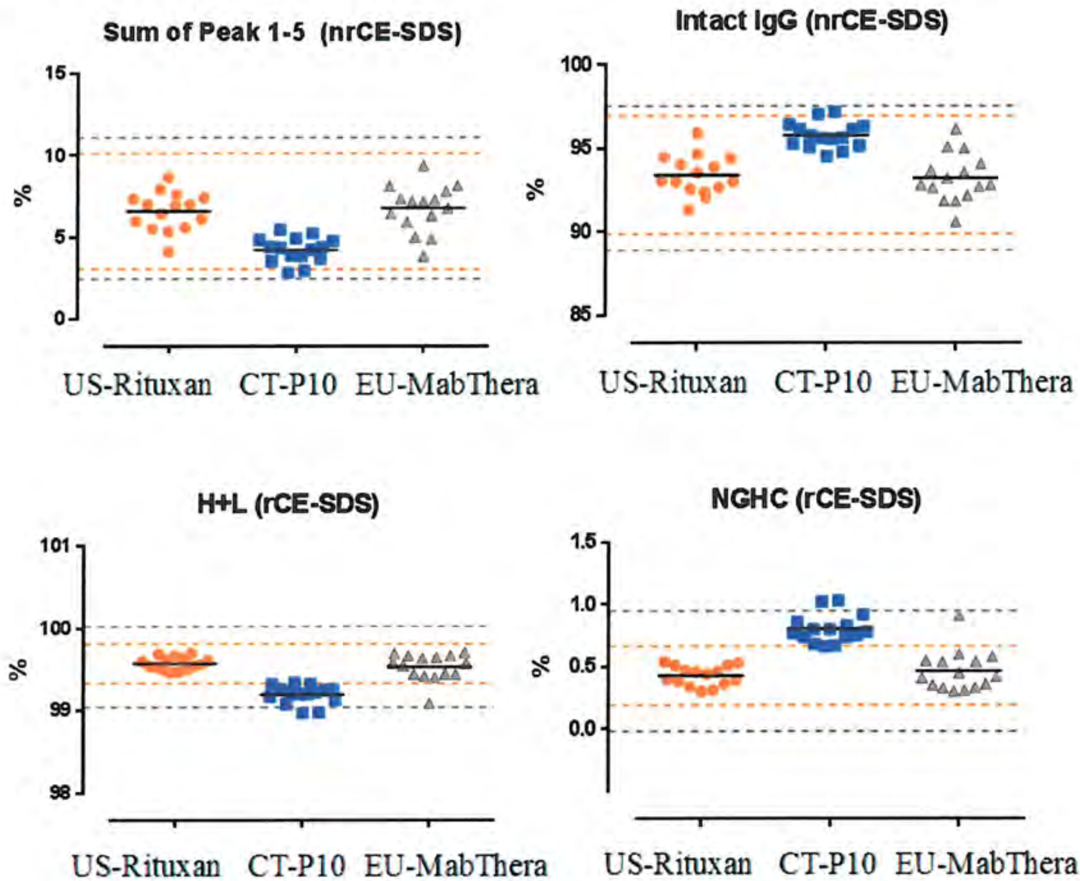
Figure 6. Reducing CE-SDS of CT-P10 Drug Product



Source: Figure excerpted from the Applicant's 351(k) BLA submission.

The average value and the range of size variants are shown in Figure 7.. For non-assembled forms of HC and LC (sum of peak 1-5), two of the 15 tested CT-P10 lots were lower than the lower limit of the QR established from the analyzed US-licensed Rituxan lots. The overall difference in the non-assembled forms of HC and LC is small and associated with lower risk because CT-P10 has fewer non-assembled forms. For NGHC, fourteen of the 15 tested CT-P10 lots were higher than the upper limit of the QR of US-licensed Rituxan. However, the differences are considered minor in the both cases. The above-described slight differences do not preclude a finding that CT-P10 is highly similar to US-licensed Rituxan.

Figure 7. Size Variants in US-licensed Rituxan, CT-P10, and EU-approved MabThera by Non-reducing and Reducing CE-SDS

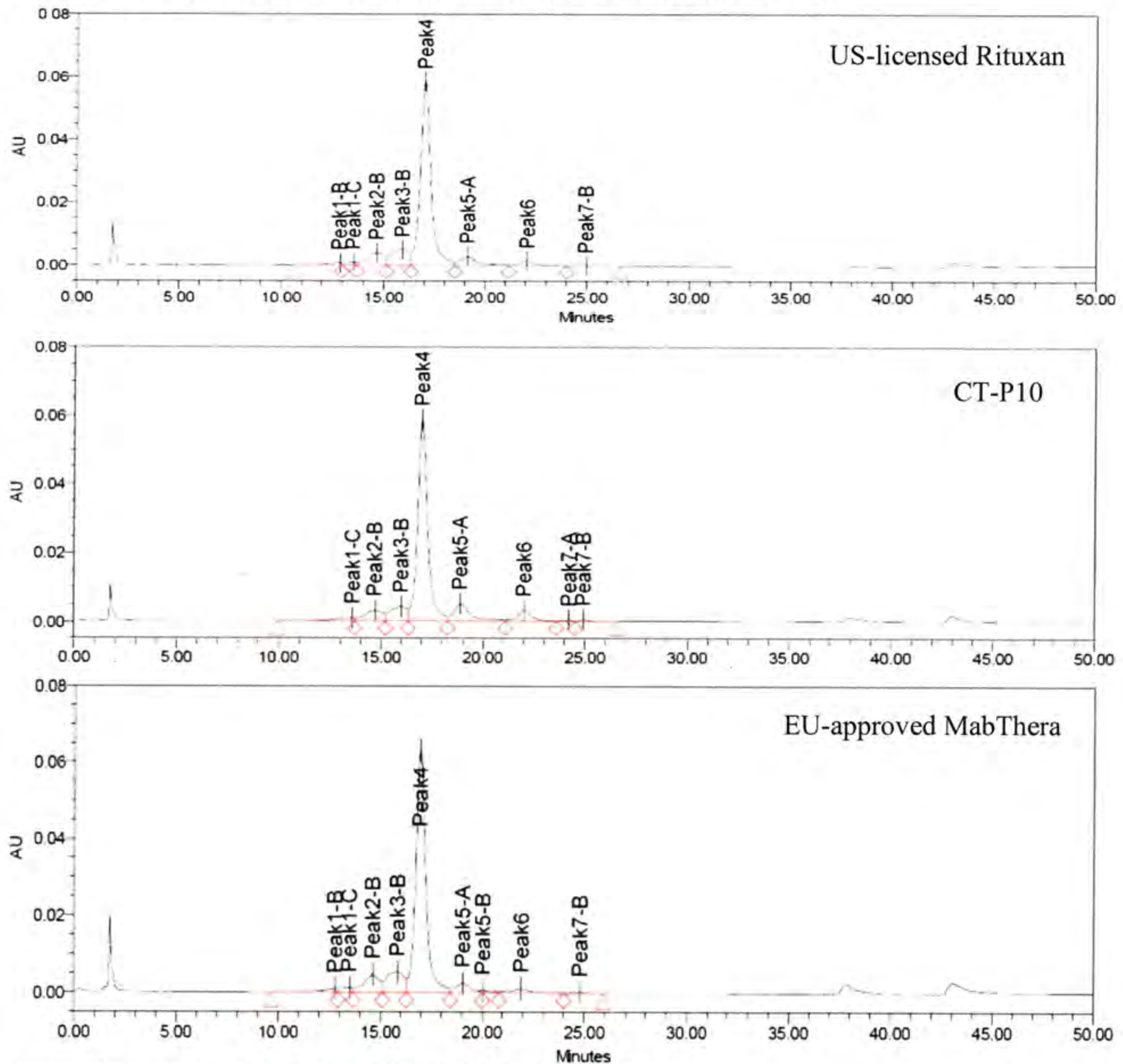


The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

Charge Variants

Charge heterogeneity in monoclonal antibodies is often derived from post-translational modifications like deamidation, oxidation, charged glycans, glycation, and variability observed in N-terminal glutamine or C-terminal lysine residues. As shown in Figure 8, the charge profiles by IEC-HPLC for US-licensed Rituxan, CT-P10, and EU-approved MabThera show three distinct regions commonly observed in monoclonal antibody products: acidic peaks (peaks 1-3), main peak (peak 4), and basic peaks (peaks 5-7).

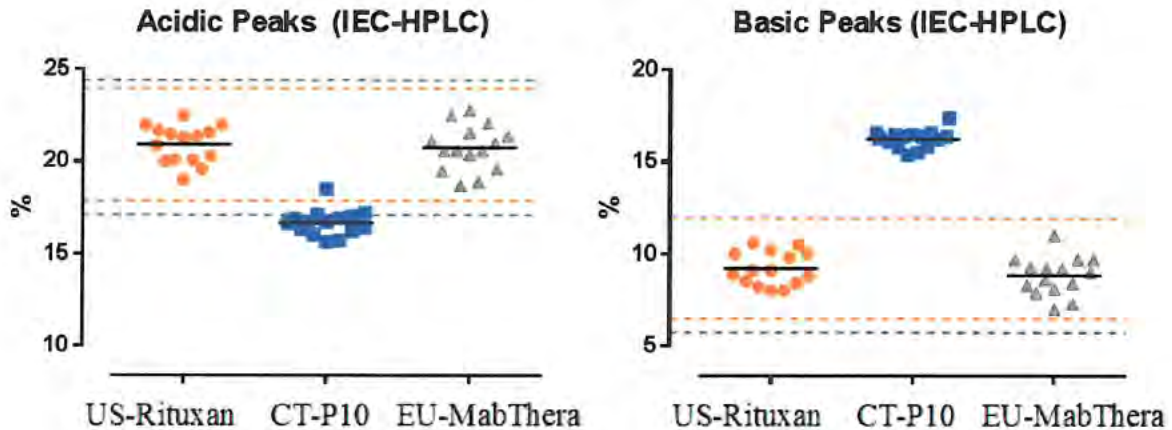
Figure 8. Chromatograms of Charge Variant Profile by IEC-HPLC



Source: Figures excerpted from the Applicant's 351(k) BLA submission.

For the main peak, CT-P10 lots are within the QR defined by the analyzed lots of US-licensed Rituxan. However, CT-P10 lots showed lower levels of acidic peaks and higher levels of the basic peaks compared to US-licensed Rituxan (and EU-approved MabThera) (Figure 9).

Figure 9. Percentage of Acidic and Basic Peaks of US-licensed Rituxan, CT-P10, and EU-approved MabThera by IEC-HPLC



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission

To elucidate the difference observed in the IEC-HPLC profiles, the Applicant performed a peak characterization study using one lot of each drug product to determine the constituents with in the acidic, main and basic peaks. The IEC-HPLC peaks 1-7 were fractionized (Figure 10) and each fraction was collected and subjected to LC/MS analysis and biological activity assessment.

Figure 10. Overlaid Chromatograms of IEC-HPLC Fractionized Peaks for Representative CT-P10 Lot (each color represents the chromatogram of one fraction)

Source: Figure excerpted from the Applicant's 351(k) BLA submission.

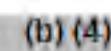
The LC/MS analysis of the purified peaks showed that in all three products the acidic peaks had enriched amounts of deamidated variants and sialylated N-glycan species, and the basic peaks

showed enriched levels of N-terminal glutamine and C-terminal lysine variants in all three products.

HC Asn55 and Asn388 are the two predominant deamidation sites for all three products and both are enriched in the acidic peaks, respectively, in peaks 1, 2 and peak 3 (Table 3). HC Asn55 is located within the complementarity determining region (CDR), however the assessment of the purified peaks shows no significant increase of CD20 binding for the fractionated peaks 1 and 2 compared to the unfractionated antibody. HC Asn388 is located outside of the Fab and Fc binding regions, which is not expected to impact product biological activities.

In addition to deamidated species, N-glycan sialylated species is also enriched in the acidic peaks. Studies have shown that N-glycan sialylation in antibodies may impact FcγR binding and decrease effector function [30, 31]. Slightly lower level of N-glycan sialylation is observed in the CT-P10 lots compared to the US-licensed Rituxan and EU-approved MabThera lots (Table 3).

Table 3. Percentage of HC Deamidation and Sialylation in the Purified Peaks from IEC-HPLC



Source: Data derived from peptide mapping results from the Applicant's 351(k) BLA submission.

The biological activity assessment of the purified peaks shows that the acidic peaks exhibited similar levels of CD20 binding, Fc effector functions, apoptosis and FcRn binding among the three products, which suggests that the difference observed in acidic peaks have minimal effect on biological activity.

A slight difference in the level of N- and C-terminal variants may contribute, in part, to the difference seen in the basic peaks. Numerous publications have shown that the C-terminal lysine is cleaved from antibody products in vivo within a short period after administration, as well these modifications have no effect on antibody structure, antigen binding and Fc-mediated functions [30], which was also confirmed by the Applicant's biological activity assessment of the purified peaks.

Overall, the difference observed in charge variants would not impact the mechanism of action of the product and do not preclude a finding that CT-P10 is highly similar to US-licensed Rituxan.

Post-Translational Modification

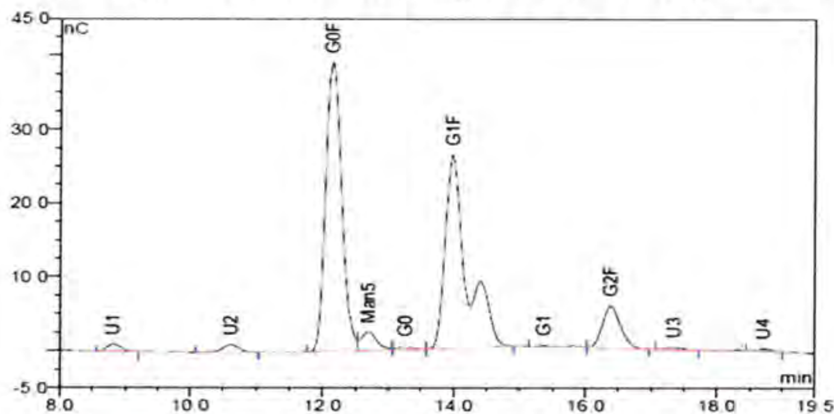
Peptide mapping by LC-MS was used to characterize the following post-translational modifications: deamidation (HC Asn55, Asn290, Asn319, Asn365, Asn388, LC Asn136), oxidation (HC Met34, Met81, Met256, Met432, LC Met21), N-terminal glutamine variants (HC Gln01, LC Gln01), and C-terminal lysine variant (HC Lys451). The deamidation levels on Asn residues are low in all three products (<3%). CT-P10 lots are mostly within the QRs established by the analyzed US-licensed Rituxan lots, except for 2-3 CT-P10 lots which were just outside of US-Rituxan QRs for Met 365 and Met388 residues. The levels of oxidation (<4%), N-terminal glutamine variants (≤5%), and C-terminal lysine variant (<3%) are similar between CT-P10 and US-licensed Rituxan. Overall, the levels of post-translation modifications are low among the three products, the described differences observed do not preclude a demonstration that CT-P10 is highly similar to US-licensed Rituxan.

Glycosylation

Rituximab products contain one N-linked glycosylation site in the Fc region of each HC of the molecule. Antibody glycosylation is typically heterogenous and is variable among antibody products and, to some extent, among lots of a specific product. Different glycan structures can modify product activity. For example, the presence of fucose on the N-glycan chain can reduce the interaction with FcγRIIIa on effector cells and reduce ADCC effect. Glycan structures can also affect pharmacokinetics of monoclonal antibodies. Specifically, high mannose glycans have been demonstrated to increase the clearance rate of a product [31, 32]. Therefore, the Applicant evaluated the glycosylation content of CT-P10, US-licensed Rituxan, and EU-approved MabThera using a HPAEC-PAD.

The results show that G0F and G1F are the most abundant N-glycans in all three products. Minor species including Man5, G1F, G0 and G1, as well as sialylated species were also detected (Figure 11).

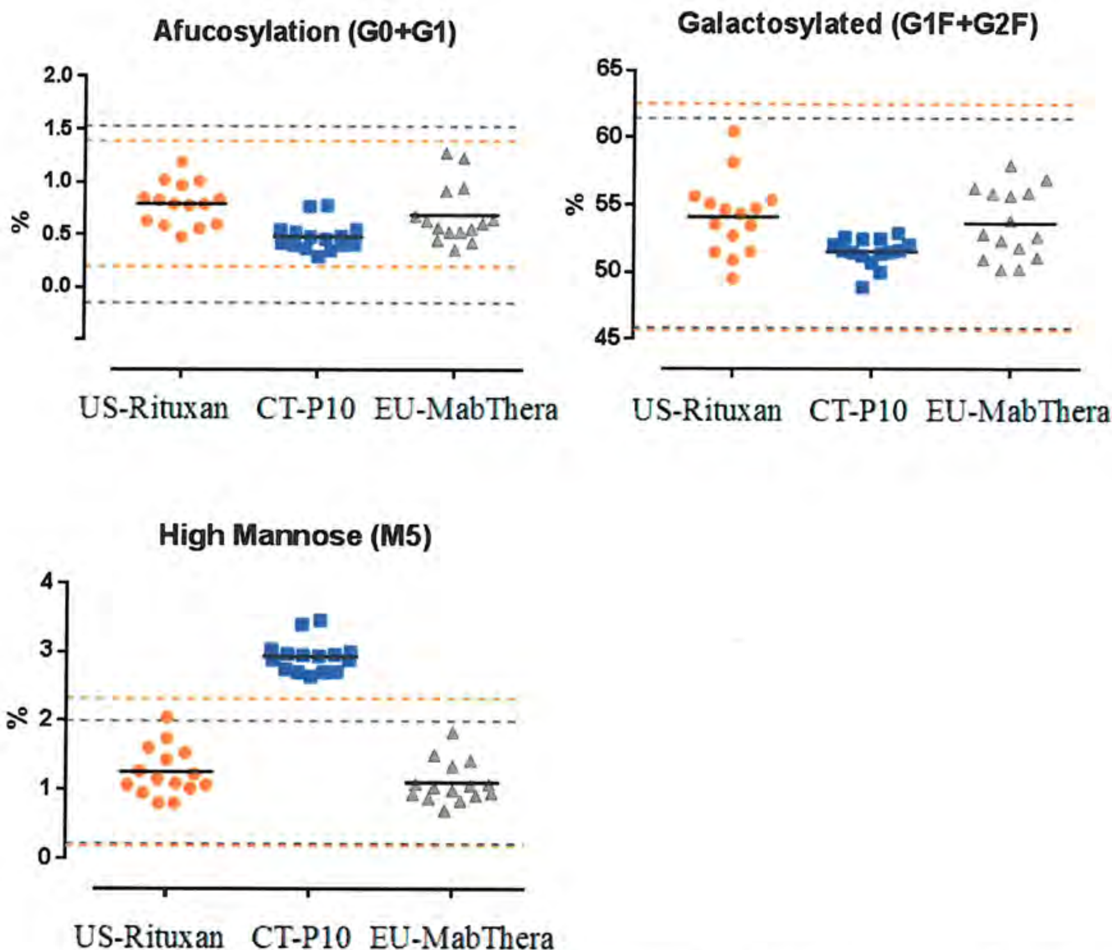
Figure 11. Representative Chromatogram of CT-P10 by HPAEC-PAD



U1 to U4 are classified as unidentified peaks by the Applicant.
Source: Figure excerpted from the Applicant's 351(k) BLA submission.

The Applicant compared the relative abundance of afucosylation (G0+G1), galactosylation (G1F+G2F), and high mannose (M5) among the three products (Figure 12). The levels of afucosylation and galactosylation for all CT-P10 lots were within the QR of US-licensed Rituxan (and the QR of EU-approved MabThera). For high mannose, CT-P10 lots show higher levels of Man5 (mean of 2.93 %) compared to US-licensed Rituxan (mean of 1.25 %) and EU-approved MabThera (mean of 1.10 %) (Figure 12). Sialic acid content was also analyzed and found to be low in all three products.

Figure 12. N-glycan Analysis of US-licensed Rituxan, CT-P10, and EU-approved MabThera by HPAEC-PAD



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

The slightly higher level of Man5 in CT-P10 compared to US-licensed Rituxan (2.93% vs 1.25%) is unlikely to result in significant difference in serum clearance [32]. Therefore, the minor difference in the relative abundance of high mannose does not preclude a finding that CT-P10 is highly similar to US-licensed Rituxan.

Biological activity

Multiple bioassays that reflect various potential mechanisms of action were employed in the similarity assessment. The bioassays include assays for CDC, ADCC, ADCP and apoptosis. CD20 target binding (measured by ELISA) and Fc binding (FcγR binding measured by SPR,

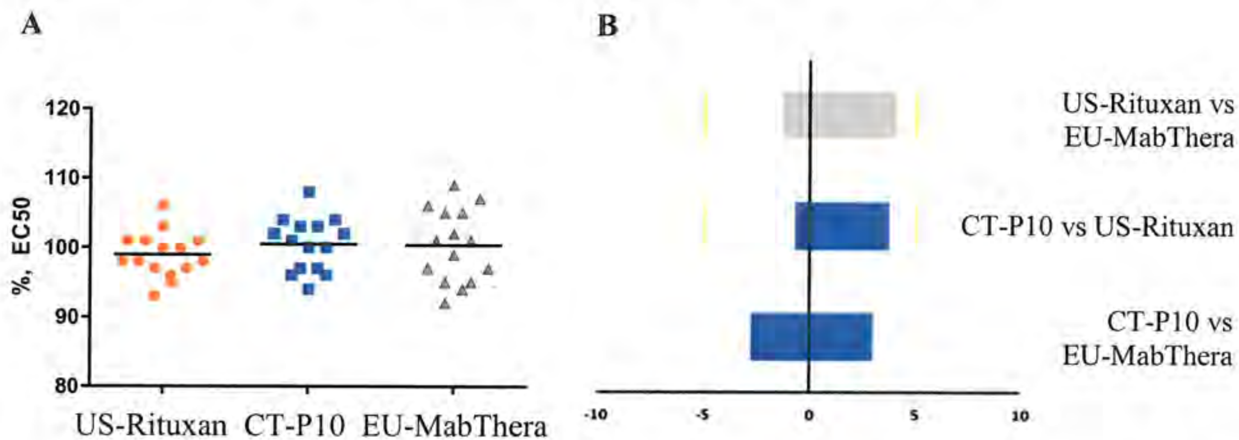
C1q binding measured by ELISA) activities were also included in the analytical similarity assessment.

The CDC and ADCC activities were each compared using an equivalence test approach. The biological activity data are reported as a percentage relative to the Applicant's in-house CT-P10 reference standard.

CDC bioassay

CDC activity of the products was assessed using a cell-based assay in which normal human serum was used as source of complement and Wil2-S cell line (CD20-expressing B-lymphoblast line) was used as target cells. Wil2-S cells were incubated with increasing concentration of CT-P10, US-licensed Rituxan and EU-approved MabThera in the presence of normal human serum. CDC activity is determined by measuring Wil2-S cell metabolic activity as an indicator of cell viability using a colorimetric method. The relative potency is evaluated in a four-parameter logistic curve model. A comparison of the relative CDC activity of CT-P10, US-licensed Rituxan and EU-approved MabThera were carried out using 15 lots of each product. The CDC activity results are plotted in Figure 13A. The numerical data and equivalence testing results are provided in Figure 13B and Table 4.

Figure 13. Scatter Plot and Equivalence Test Results for CDC Activity



The black horizontal bars represent the mean percentages.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

The dotted yellow line and grey lines represent the EM of US-Rituxan and EU-MabThera, respectively. Results are presented as 90 % CI of mean difference between 2 products. Source: Figure excerpted from the Applicant's 351(k) BLA submission.

Table 4. Equivalence Test Results for CDC Activity

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI		
CT-P10 vs Rituxan	(15, 15)	1.53	(-0.69, 3.75)	(-4.93, 4.93)	Yes
CT-P10 vs MabThera	(15, 15)	0.13	(-2.74, 3.01)	(-7.91, 7.91)	Yes
MabThera vs Rituxan	(15, 15)	1.40	(-1.35, 4.15)	(-4.93, 4.93)	Yes

Source: FDA analysis of data from the Applicant's 351(k) BLA submission.

The statistical equivalence analyses shown in Table 4 support that the CDC activity of CT-P10 is equivalent to that of US-licensed Rituxan.

ADCC bioassays

ADCC activity of the products was assessed using a cell-based assay in which Raji cells (CD20-expressing B lymphoblast cell line) were used as target cells and human PBMCs were used as effector cells. Dye-labelled Raji cells were pre-incubated with three different concentrations of the product samples (0.122 μg/mL, 0.035 μg/mL, and 0.010 μg/mL) within the linear range of the drug dose-response curve, followed by incubation with PBMCs. The CT-P10-, US-licensed Rituxan- and EU-approved MabThera-induced ADCC effect on Raji cells is measured by release of the cell dye that are quantified using a fluorescence detection. These data were subjected to a statistical analysis using equivalence testing. The ADCC activity results and equivalence testing results for are shown in Figure 14 and Table 5.

Figure 14. Scatter Plot and Equivalence Test Results for ADCC Activity

The black horizontal bars represent the mean percentages.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

The dotted yellow line and grey lines represent the EM of US-Rituxan and EU-MabThera, respectively. Results are presented as 90 % CI of mean difference between 2 products.
Source: Figure excerpted from the Applicant's 351(k) BLA submission.

Table 5. Equivalence Test Results for ADCC Activity

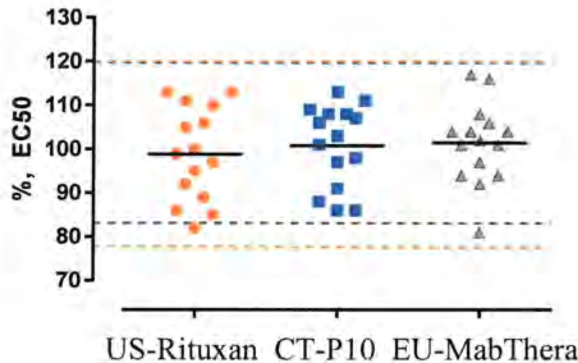
Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI		
0.122 μg/mL product					
CT-P10 vs Rituxan	(15, 15)	-0.87	(-3.62, 1.89)	(-5.96, 5.96)	Yes
CT-P10 vs MabThera	(15, 15)	0.00	(-2.98, 2.98)	(-7.10, 7.10)	Yes
MabThera vs Rituxan	(15, 15)	-0.87	(-3.58, 1.85)	(-5.96, 5.96)	Yes
0.035 μg/mL product					
CT-P10 vs Rituxan	(15, 15)	-3.07	(-7.56, 1.43)	(-11.19, 11.19)	Yes
CT-P10 vs MabThera	(15, 15)	-1.53	(-6.00, 2.94)	(-11.09, 11.09)	Yes
MabThera vs Rituxan	(15, 15)	-1.53	(-6.15, 3.08)	(-11.19, 11.19)	Yes
0.010 μg/mL product					
CT-P10 vs Rituxan	(15, 15)	0.73	(-4.75, 6.22)	(-11.11, 11.11)	Yes
CT-P10 vs MabThera	(15, 15)	2.67	(-2.47, 7.80)	(-8.76, 8.76)	Yes
MabThera vs Rituxan	(15, 15)	-1.93	(-6.08, 2.22)	(-11.11, 11.11)	Yes

Source: FDA analysis of data from the Applicant's 351(k) BLA submission.

The statistical equivalence analyses shown in Table 5 support that the ADCC activity of CT-P10 is equivalent to that of US-licensed Rituxan.

An ADCC reporter assay was also used to assess activation of NFAT (nuclear factor of activated T cells) pathway in effector cells which is one of the downstream signaling of FcγR binding to antibody Fc. In this assay, Raji cells were used as target cells and Jurkat cells engineered to express NFAT-RE (response element)-Luciferase and FcγRIIIa were used as effector cells. The relative ADCC reporter activity for analyzed US-licensed Rituxan, CT-P10, and EU-approved MabThera lots are shown in Figure 15. Statistical analysis showed that all CT-P10 lots were within the Applicant-determined QRs (calculated as mean ± 2SD due to high criticality) of US-licensed Rituxan and EU-approved MabThera lot.

Figure 15. Scatter Plot Results for ADCC Reporter Assay



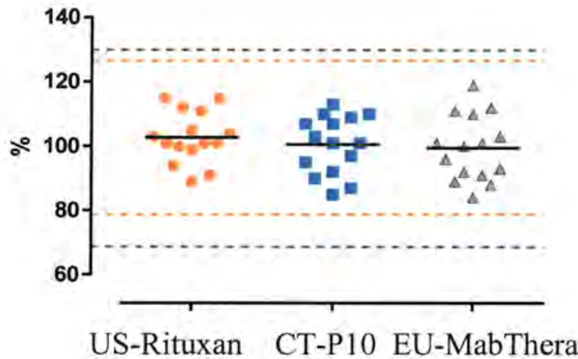
The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 2SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

ADCP bioassay

ADCP activity was assessed using a cell-based assay in which Raji cells were used as target cells and primary monocyte-derived macrophages were used as effector cells. Raji cells were labelled with a fluorescent marker (PKH67-FITC), followed by incubation with the product samples at three different concentrations (1.56 ng/mL, 6.25 ng/mL, 25.0 ng/mL) within the linear range of the drug dose-response curve. Monocytes were isolated from human PBMCs and were differentiated into macrophages. The macrophages were added into a cell-antibody mixture, and the phagocytic activity was assessed by flow cytometry analysis after staining the macrophages with CD11b-APC. The phagocytotic activity was assessed by calculation of double-positive stained macrophages with respect to total target cells using flow cytometry.

The ADCP activity of the analyzed US-licensed Rituxan, CT-P10, and EU-approved MabThera lots is shown in Figure 16. Statistical analysis showed that the relative ADCP activity of CT-P10 lots was within the QR of US-licensed Rituxan and EU-approved MabThera lots.

Figure 16. Scatter Plot Results for ADCP Activity

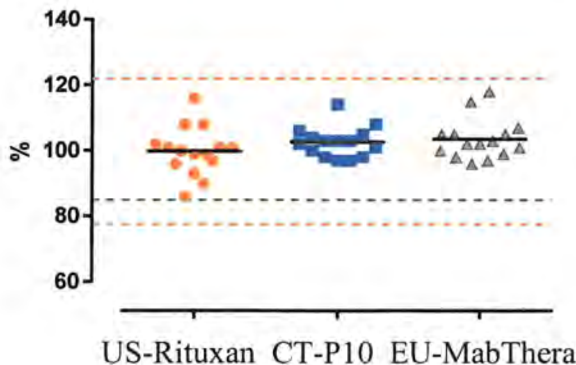


Representative data for 6.25 ng/mL concentration for each product.
The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

Apoptosis bioassay

CD20-induced cell apoptosis was assessed using Raji cells. After pre-incubation with the product samples, cells were harvested, labelled by annexin-V conjugate and subjected to flow cytometry. The apoptotic activity was determined at 0.13 μg/mL, 0.04 μg/mL, 0.01 μg/mL product concentrations that are within the linear range of the response. The apoptosis data of the analyzed US-licensed Rituxan, CT-P10, and EU-approved MabThera lots are shown in Figure 17. Statistical analysis showed that the relative apoptotic activities of all tested CT-P10 lots were within the QRs defined by US-licensed Rituxan and EU-approved MabThera lots.

Figure 17. Scatter Plot Results for Apoptotic Activity



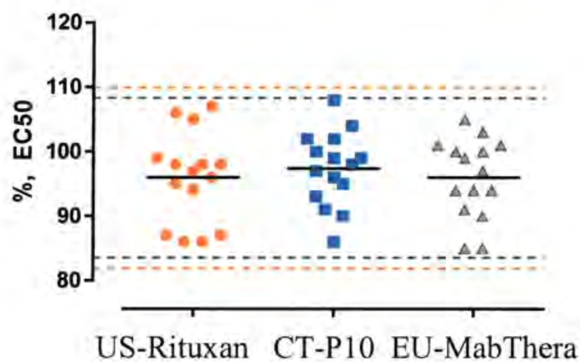
Representative data for 0.04 μg/mL concentration for each product.

The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

CD20 binding ELISA

CD20 binding was assessed by a cell-based CD20 ELISA using CHO-K1 cells expressing recombinant CD20. The relative CD20 binding affinities of the tested CT-P10, US-licensed Rituxan and EU-approved MabThera lots, 15 lots each, are plotted in Figure 18. The results for all CT-P10 lots are within the Applicant-determined QRs (calculated as mean ± 2SD due to high criticality) of the US-licensed Rituxan and EU-approved MabThera lots, respectively.

Figure 18. Scatter Plot Results for CD20 Binding

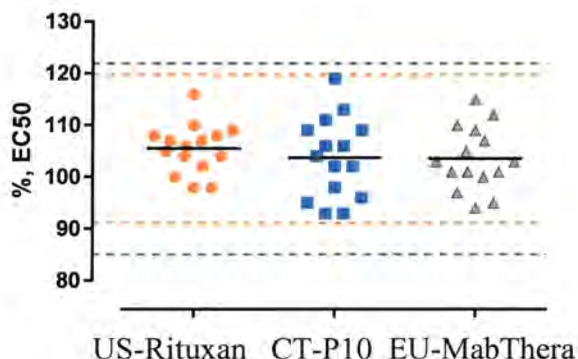


The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 2SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

C1q binding ELISA

Binding of C1q to Fc of antibody initiates the complement cascade that leads to CDC of the target cell. The Applicant evaluated the affinity for C1q binding by a sandwich ELISA. The relative C1q binding affinity of the tested CT-P10, US-licensed Rituxan and EU-approved MabThera lots, 15 lots each, is plotted in Figure 19. The results for all CT-P10 lots are within the QRs of the US-licensed Rituxan and EU-approved MabThera lots, which are consistent with the results from CDC assay.

Figure 19. Scatter Plot Results for C1q Binding



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
Source: FDA analysis of the Applicant's 351(k) BLA submission.

Fc Receptors binding affinity by SPR

The Fc receptors, FcγRI, FcγRII, FcγRIII and FcRn, are diverse in structure and cell type expression [20, 33]. The predominant Fc receptor type on NK cells is FcγRIII (a and b forms), which binds to Fc of antibody and leads to ADCC activity. Other immune effector cells, such as macrophages and monocytes, express a broad range of FcγRs, which can lead to effector functions, such as ADCP, ADCC and release of inflammatory mediators through binding to Fc [20]. The neonatal Fc receptor, FcRn, plays an important role in IgG homeostasis, by binding the Fc region and protecting the molecule from lysosomal degradation, thus prolonging the half-life of the antibody.

Binding of FcγRs and FcRn was assessed using a SPR-based assay, in which recombinant Fc receptors are coupled to a sensor chip. The relative binding affinity is determined by comparing the equilibrium constant for dissociation (K_D) of each sample to that of in-house reference standard. The relative binding affinity of the tested CT-P10, US-licensed Rituxan and EU-approved MabThera lots, 15 lots each, are plotted in Figure 20. The results for all CT-P10 lots are within the QRs of the US-licensed Rituxan and EU-approved MabThera lots for each Fc receptor and considered visually similar for FcγRI.

Figure 20. Scatter Plot Results for Fc Receptor Binding Affinity

FcγRIIIa-V

130
120
110
100
90
80
%, K_D
US-Rituxan CT-P10 EU-MabThera

FcγRIIIa-F

160
140
120
100
80
60
%, K_D
US-Rituxan CT-P10 EU-MabThera

FcγRIIIb

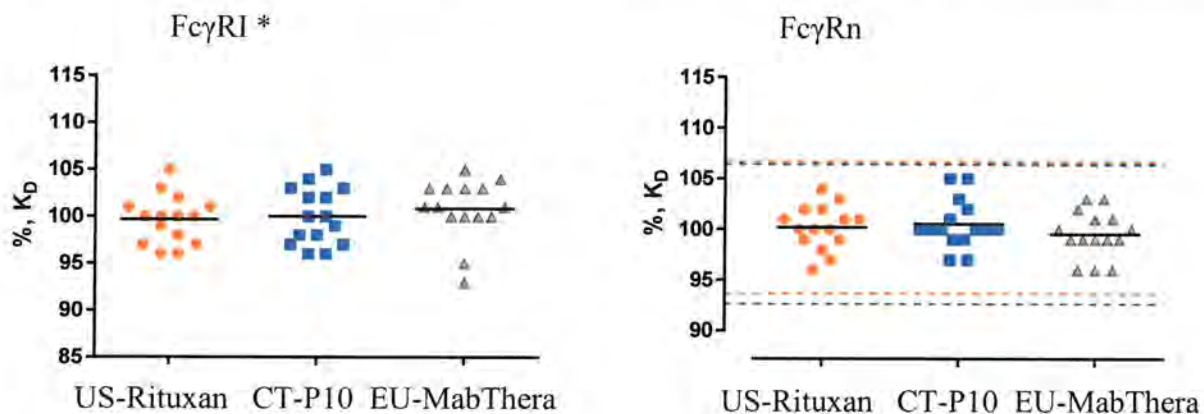
140
120
100
80
60
%, K_D
US-Rituxan CT-P10 EU-MabThera

FcγRIIa

115
110
105
100
95
90
85
%, K_D
US-Rituxan CT-P10 EU-MabThera

FcγRIIb

120
110
100
90
80
70
%, K_D
US-Rituxan CT-P10 EU-MabThera



The black horizontal bars represent the mean percentages. The dotted orange lines and grey lines represent the QR limits based on mean ± 3SD of the US-Rituxan and EU-MabThera lots, respectively.
* Similarity assessment for FcγRI is by visual comparison.
Source: FDA analyses of the Applicant's 351(k) BLA submission.

Comparative Stability Studies

The Applicant evaluated stability of CT-P10, US-licensed Rituxan, and EU-approved MabThera lots under thermal, oxidative, UV light, acidic, and basic stress conditions. The stressed samples were evaluated by peptide mapping (LC/MS), SEC-HPLC, reducing and non-reducing CE-SDS, IEC-HPLC, IEF, oligosaccharide profiling, and biological activity tests (FcRn binding, FcγRIIIa binding, C1q binding, and CD20 binding) to assess the physicochemical and functional changes. The results of the comparative stability studies support that under the tested conditions CT-P10, US-licensed Rituxan, and EU-approved MabThera have similar stability profiles.

As part of the analytical similarity assessment, the Applicant performed assessments for sub-visible particles and process-related impurities. The data show that CT-P10 drug product lots do not contain higher process impurities and sub-visible particles compared to US-licensed Rituxan and EU-approved MabThera lots.

Conclusions from the Comparative Analytical Data

The Applicant analytically compared CT-P10 to US-licensed Rituxan using an array of biochemical, biophysical, and functional assays. These methods were used to assess primary structure, higher order structures, product-related variants, and biological activities as measured by multiple assays that reflect the known and potential mechanisms of action of US-licensed Rituxan. Size variants, charge variants, and some post-translational modifications including high mannose glycans were found to be slightly different between CT-P10 and US-licensed Rituxan lots. However, based on the supportive analytical studies and justifications provided by the Applicant, these differences were adequately addressed. In considering the comparative analytical studies in their entirety, the FDA concludes the data submitted supports a

demonstration that CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically-inactive components.

4. Pharmacology/Toxicology

Executive Summary

The Applicant submitted two nonclinical studies in support of this BLA. Of note, the Applicant had existing clinical data and experience with CT-P10 at the time of initiating clinical studies under US IND.

The primary nonclinical study was a comparative 8-week repeat-dose toxicity study in cynomolgus monkeys; the purposes of this study were to compare the toxicity, PK, and PD profiles of CT-P10 and EU-MabThera. CT-P10 and EU-MabThera were immunogenic in monkeys, and some monkeys exhibited symptoms of hypersensitivity. The study was terminated early due to animal welfare concerns. Clinical signs, histopathology, and changes in hematology parameters were similar between treatment arms, and were consistent with the known toxicological profile of rituximab. The PK and PD profiles of CT-P10 and EU-MabThera were comparable. The Applicant also conducted a tissue cross-reactivity study with a panel of human tissues; CT-P10 and EU-MabThera demonstrated similar staining profiles with only minor differences in staining intensity.

Conclusion

The results of the comparative repeat-dose toxicity study in cynomolgus monkeys, and tissue cross-reactivity study support the demonstration of biosimilarity between CT-P10 and US-licensed Rituxan. No residual uncertainties have been identified by the Pharmacology and Toxicology discipline.

5. Immunogenicity

Executive Summary

The incidence of immunogenicity for CT-P10 and US-Rituxan was compared in a multiple-dose, parallel-arm study in subjects with RA (Study CT-P10 3.2). Study CT-P10 3.2 was designed as a PK similarity study (Part 1), a comparative clinical study (Part 2), and a study to assess safety and immunogenicity in patients undergoing a single transition from US-licensed Rituxan to CT-P10 (Part 3). FDA determined that the comparative immunogenicity data from Study CT-P10 3.2 was sufficient to inform upon an adequate immunogenicity assessment to support a demonstration of biosimilarity to US-Rituxan. Immunogenicity assessments were also included in the oncology studies (Study CT-P10 3.3 and 3.4) but were not adequate because drug

concentrations were higher than the threshold for drug interference at the low positive control for the immunogenicity assay.

In Study CT-P10 3.2, the results of the Main Study Period (i.e., through Week 48) indicate similar incidence and titers of anti-drug antibodies (ADA) for CT-P10 and US-licensed Rituxan. No apparent impact of ADA on safety or pharmacokinetic parameters was observed. In the Extension Period, where patients on US-licensed Rituxan were randomized to either remain on US-licensed Rituxan or undergo a single transition to CT-P10 (up to 76 weeks), overall a small number of patients developed new ADAs.

Therefore, the data indicate that there is no increase in immunogenicity risk for CT-P10 as compared to that of US-Rituxan, and no increased safety risk with a single transition from US-licensed Rituxan to CT-P10.

Background

Immune responses against therapeutic biological products can negatively impact the safety, efficacy, and pharmacokinetics of the product. Often, immune responses to therapeutic biologics are measurable in the form of anti-drug antibodies (ADA) that can be detected in serum following exposure to the drug. Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of ADA in the studies described below with the incidence of ADA in other studies or to other products may be misleading.

Methods

The development of ADA was monitored in Study CT-P10 3.2, a multiple-dose, parallel arm design clinical study that allowed for a comparative assessment of immunogenicity between CT-P10 and US-Rituxan in a sensitive population. The study design, patient population, treatment, and immunogenicity sampling schedule of the study is summarized in Table 6.

Table 6. Immunogenicity sampling in Study CT-P10

Study ID	Design	Route	Number	Population	Dose/ Schedule	Sampling
CT-P10 3.2	Parallel	IV	CT-P10 (N = 161) US-Rituxan (N = 151)	RA	1000 mg co-administered with methotrexate up to 2 courses* in the main study (parts 1 and 2) and 1 additional course in the extension portion	Weeks 0 (pre-dose, baseline), 24, and 48

Source: Summary based on information from the CT-P10 351(k) BLA submission. *Each course of treatment consists of 2 infusions with a 2-week interval

Serum samples were tested for ADA using a tiered strategy as recommended by FDA (Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. CDER, CBER, and CDRH. April 2016). [34] A screening assay was used to test all samples. Samples deemed positive in the screening assay were then tested in a confirmatory assay to confirm that the binding was specific for the product. Samples confirmed positive were titered and assessed for neutralizing activity.

Results

The immunogenicity results of the multiple-dose, parallel-arm comparative clinical Study CT-P10 3.2 are summarized in Table 7. The baseline (Week 0) immunogenicity incidence was high for each arm, which may be attributed to the disease, prior treatments, and/or other factors.

Table 7. Immunogenicity by ADAs and nAbs in Study 3.2, Main Study Period

Immunogenicity Sampling Time	Parameter	CT-P10 (N=161)	US-Rituxan (N=151)
Week 0	ADA positive, n /N (%)	19/161 (11.8)	13/151 (8.6)
	nAb positive, n (%)	1 (5.3)	0 (0)
Week 24	ADA positive, n/N (%)	24/145 (16.6)	33/141 (23.4)
	nAb positive, n (%)	0 (0)	1 (0.3)
Week 48	ADA positive, n/N (%)	7/142 (5)	13/136 (9.6)
	nAb positive, n (%)	1 (14.2)	1 (7.7)

Source: FDA analysis from the CT-P10 351(k) BLA submission

There was no apparent impact of immunogenicity on safety or PK parameters from Study CT-P10 3.2 (data not shown).

Conclusion

Similar immunogenicity results were observed in Study CT-P10 3.2 for CT-P10 and US-Rituxan. The data support a determination of no clinically meaningful differences between CT-P10 and US-Rituxan.

6. Clinical Pharmacology

Executive Summary

The objectives of the clinical pharmacology program are to evaluate the pharmacokinetic (PK) similarity between CT-P10 and US-licensed Rituxan to support a demonstration of no clinically meaningful differences, and to add to the totality of the evidence to support a demonstration of biosimilarity between CT-P10 and US-licensed Rituxan.

The Applicant submitted Study CT-P10 3.2 which evaluated the pharmacokinetic (PK) similarities of CT-P10 and US-licensed Rituxan. Pharmacokinetic data from Study CT-P10 3.3, Part 1 and Study CT-P10 3.4 were also submitted and are considered as supportive.

Part 1 of Study CT-P10 3.2 was a randomized, double-blind, parallel-group study designed to compare PK of CT-P10 (n = 64) and US- licensed Rituxan (n = 65) administered as two-1000 mg intravenous infusion in subjects with rheumatoid arthritis (RA). The 90% confidence intervals (CI) for the ratio of geometric means for the pairwise comparisons of AUC_{0-14d}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the pre-specified limits of 80 – 125%. The results of study CT-P10 3.2 established PK similarity between CT-P10 and US- licensed Rituxan. For Study CT-P10 3.3 and Study CT-P10 3.4, the PK results of CT-P10 were comparable to the PK results of US-Rituxan.

Overall, clinical pharmacology information supports a demonstration of PK similarity between CT-P10 and US-licensed Rituxan which supports a demonstration of no clinically meaningful differences, and adds to the totality of the evidence to support a demonstration of biosimilarity of CT-P10 and US-licensed Rituxan.

Description of Clinical Pharmacology Studies

Part 1 of Study CT-P10 3.2 was a randomized, double-blind, parallel-group study designed to compare PK of CT-P10 (n = 64) and US-Rituxan (n = 65) administered as two-1000 mg intravenous (IV) infusions in subjects with RA. The primary PK endpoints were AUC_{0-14d}, AUC_{0-t}, and $AUC_{0-\infty}$.

Based on the Guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," [35] a parallel group study design in subjects with RA (Study CT-P10 3.2) is considered adequate to provide primary PK similarity data for the pharmacokinetic assessment of proposed biosimilars to US-Rituxan because US-Rituxan

has a long half-life (~18 days in RA subjects). Conducting the PK assessment in patients with RA was considered safe and the RA population is considered adequately sensitive for such an assessment.

The PK of CT-P10 was also compared to that of US-Rituxan in a randomized, double-blind, 2-arm, parallel-group study conducted in patients with advanced follicular lymphoma (AFL) (Study CT-P10 3.3). CT-P10 (n = 59) or US-Rituxan (n = 62) was administered as weekly 375 mg/m^2 IV infusions with concomitant drugs every 3 weeks up to 8 cycles to patients with AFL.
The AUC_{tau} and C_{max} following Cycle 4 for CT-P10 and US-Rituxan were compared.

The C_{max} and C_{trough} were compared in patients with low tumor burden follicular lymphoma (LTBFL) in Study CT-P10 3.4 administered CT-P10 (n = 130) or US-Rituxan (n = 128) as monotherapy. These patients received weekly 375 mg/m^2 IV infusions for 4 weeks (induction period) and every 8 weeks thereafter, up to a maximum 6 cycles (maintenance period).

Results of Clinical Pharmacology Study

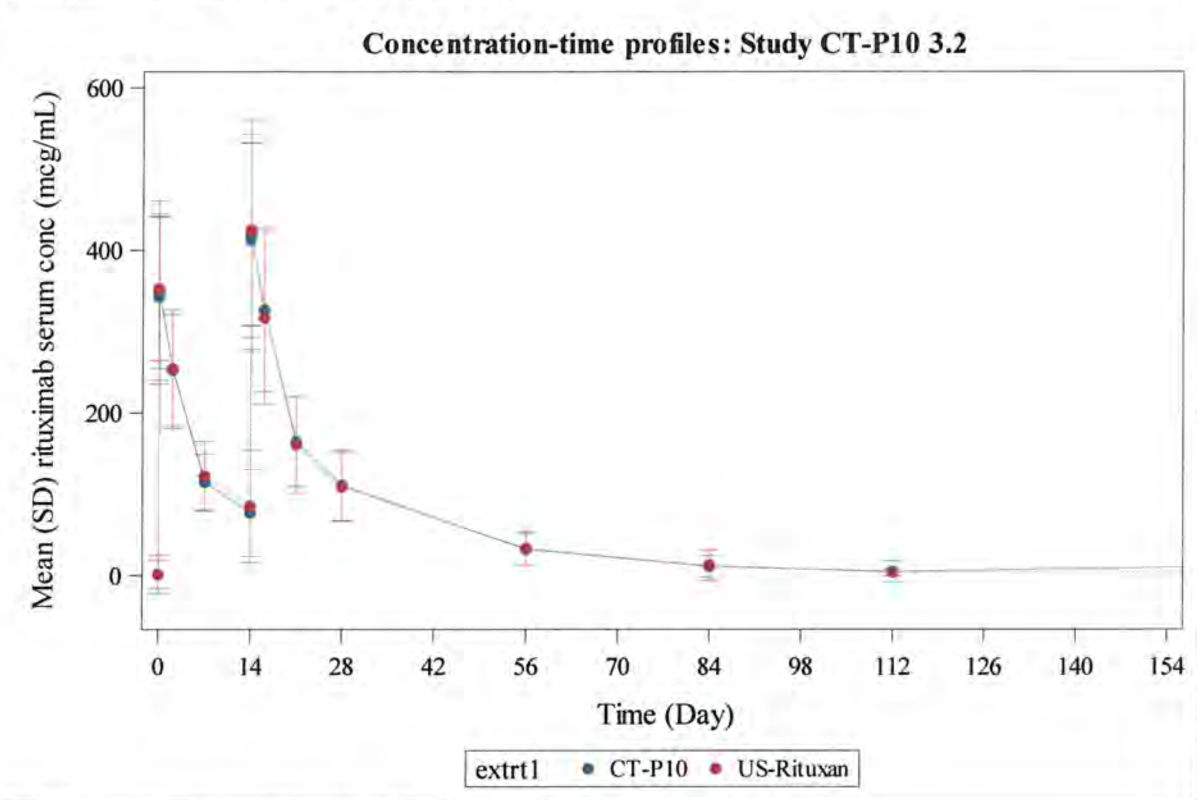
In Study CT-P10 3.2, the 90% CIs for the ratios of the geometric mean of $AUC_{0\text{-}14d}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ in pairwise comparisons between CT-P10 and US-Rituxan were within the pre-specified limits of 80% to 125% for PK similarity, as summarized in Table 8. The mean concentration-time profiles following the administration of CT-P10 or US-Rituxan in subjects with RA are shown in Figure 21. These data establish the PK similarity between CT-P10 and US-Rituxan.

Table 8. Statistical analyses of PK parameters in Study CT-P10 3.2

	Geometric mean ratio of CT-P10 compared to US-Rituxan (90% CI) *
Primary parameter	
$AUC_{0\text{-}14d}$	98.9 (90.8 - 108)
$AUC_{0\text{-}last}$	98.5 (88.7 - 110)
$AUC_{0\text{-}inf}$	97.1 (87.9 - 107)
Secondary parameter	
C_{max}	96.7 (90.3 - 104)

* presented as a percent.
Source: FDA analysis of data from CT-P10 351(k) BLA submission

Figure 21. Mean (±SD) concentration-time profiles following CT-P10 or US-Rituxan in patients with RA (Study CT-P10 3.2)



Source: FDA analysis of data from CT-P10 351(k) BLA submission

In Study CT-P10 3.3 (patients with AFL), AUC_{tau} and C_{max} for CT-P10 were comparable to AUC_{tau} and C_{max} for US-licensed Rituxan following multiple dosing (Cycle 4) (data not shown).

In Study CT-P10 3.4 (patients with LTBFL), there were no apparent differences in C_{max} and C_{trough} values between CT-P10 and US-licensed Rituxan for the evaluated cycles (Induction Cycles 1-4, and Maintenance Cycles 1-2) (data not shown).

Clinical Pharmacology Summary

Overall, the submitted clinical pharmacology information adequately demonstrated PK similarity between CT-P10 and US-Rituxan. Study CT-P10 3.2 conducted in patients with RA, using an IV administration route, is considered sufficiently sensitive to detect clinically significant differences in PK among the products and hence support a demonstration of no clinically meaningful differences between CT-P10 and US-Rituxan.

7. Efficacy

Executive Summary

Celltrion submitted two clinical studies that compared CT-P10 to US-Rituxan in the oncology setting. Both studies were randomized, double-blinded, parallel group studies that enrolled subjects with either advanced follicular lymphoma (Study CT-P10 3.3) or low tumor burden follicular lymphoma (Study CT-P10 3.4).

Description of Studies

The Applicant submitted the results from two clinical studies that compared clinical outcomes of CT-P10 with US-Rituxan and evaluated safety endpoints in patients with Non-Hodgkin's Lymphoma (NHL): CT-P10 3.3 and CT-P10 3.4. Both were randomized, double-blind, parallel group studies intended to compare CT-P10 to US-Rituxan administered intravenously. A summary of the two clinical studies is provided in the table below.

Table 9. Summary of Clinical Studies Conducted in Patients with NHL

Study ID	Design	Number in ITT	Subjects	Dose	Schedule	Primary Endpoint
CT-P10 3.3	Parallel	140	Patients with AFL	375 mg/m^2	Q3w x 8/ Maintenance	PK ORR over 24w
CT-P10 3.4	Parallel	258	Patients with LTBFL	375 mg/m^2	Qw x 4/ Maintenance	ORR at 7 months

Abbreviations: AFL = advanced follicular lymphoma, LTBFL = low tumor burden follicular lymphoma, Q3w = every 3 weeks, Qw= weekly, ORR = Overall Response Rate
Source: Summary based on information from Celltrion 351(k) BLA submission

Study CT-P10 3.3

CT-P10 3.3 was a randomized, double-blind, parallel group, active-controlled, comparative study in which patients with advanced follicular lymphoma (AFL) were randomized in a 1:1 ratio to receive either CT-P10 or US-Rituxan in combination with CVP (cyclophosphamide, vincristine, prednisone) chemotherapy. The primary endpoints were designed to demonstrate similarity in pharmacokinetics (Part 1), as well as non-inferiority in efficacy (Part 2). During the Core Study Period, all subjects received either CT-P10 or Rituxan (375 mg/m^2 IV) in combination with CVP chemotherapy every 3 weeks for up to 8 cycles. Subjects who experienced CR, CRu or PR after Cycle 8 qualified for the Maintenance Study Period where they received study drug every 8 weeks for a maximum of 12 cycles (up to 2 years).

Study CT-P10 3.4

CT-P10 3.4 was a randomized, double-blind, parallel group, comparative study in which subjects with low tumor burden follicular lymphoma (LTBFL) were randomized in a 1:1 ratio to receive either CT-P10 or US-Rituxan as monotherapy. The primary endpoint was ORR (CR+CRu+PR) at

7 months (prior to maintenance cycle 3). During the Induction Period, all subjects received either CT-P10 or US-Rituxan (375 mg/m^2 IV) once weekly for 4 weeks. Subjects who experienced CR, CRu, PR or stable disease qualified for the Maintenance Study Period where they received study drug every 8 weeks for a maximum of 12 cycles (up to 2 years).

In both clinical studies, patient demographics and baseline disease characteristics were evenly distributed between treatment arms.

GCP Compliance

The Applicant disclosed that one clinical investigation site in Study CT-P10 3.3 was identified as Good Clinical Practice (GCP) non-compliant due to scientific misconduct and was closed. The patients enrolled at this site were excluded from all analysis populations except for the sensitivity analysis for the primary PK endpoint, where they were included. In Study CT-P10 3.4, there were no GCP non-compliance issues identified.

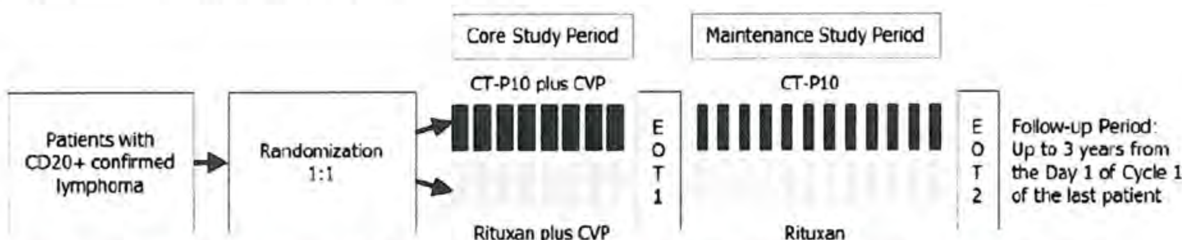
Analysis of Comparative Clinical Study Data

Study CT-P10 3.3

Study Design

The study diagram for Study CT-P10 3.3 is summarized in Figure 22. The patients were randomly assigned to either CT-P10 + CVP or US-Rituxan + CVP. Randomization was stratified by country, gender, and Follicular Lymphoma International Prognostic Index (FLIPI) score (0-2 vs. 3-5).

Figure 22. Design of Study CT-P10 3.3



Abbreviations: CD20+, cluster of differentiation 20 positive; CVP, cyclophosphamide, vincristine, and prednisone; EOT1, first end-of-treatment visit; EOT2, second end-of-treatment visit.

Source: Figure 9-1, Clinical Study Report, Study CT-P10 3.3

Cyclophosphamide (750 mg/m^2 intravenous (IV), vincristine (1.4 mg/m^2 [up to a maximum of 2mg] IV), and prednisone (40 mg/m^2 oral) (CVP) were co-administered along with the study drug. There was a Core Study Period of 8 cycles (each cycle of 21 ± 3 days) in which the CT-P10 or US-Rituxan (375 mg/m^2 IV) and CVP were administered. Up to 8 treatment cycles of -P10 or US-Rituxan were administered after which patients were evaluated for disease response.

Patients who had a response after Cycle 8 of the Core Study Period (as assessed at the first End of Treatment [EOT] Visit) were eligible to continue treatment in the Maintenance Study Period in which CT-P10 or US-Rituxan (375 mg/m^2 IV) were administered as monotherapy. Subjects received CT-P10 or US-Rituxan every 2 months for a maximum of 2 years (12 cycles). Subjects who were not eligible for the Maintenance Study Period entered the Follow-up Period.

The overall objective of this study was to demonstrate similar pharmacokinetics and non-inferior efficacy of CT-P10 compared to US-Rituxan. With this purpose, this study was divided into 2 parts.

The primary objective of Part 2 was to demonstrate that CT-P10 is non-inferior to US-Rituxan in terms of efficacy as determined by overall response rate (ORR) (the proportion of responders who achieved complete response [CR], unconfirmed complete response [CRu], or partial response [PR]) over 8 cycles of the Core Study Period according to the 1999 International Working Group (IWG) criteria in previously untreated patients with advanced (stage III-IV) cluster of differentiation 20 positive (CD20+) follicular lymphoma.

The secondary objectives of Part 2 were as follows:

- To demonstrate ORR (the proportion of responders who achieved CR or PR) over 8 cycles in the Core Study Period according to the 2007 IWG criteria.
- To evaluate additional efficacy parameters (progression-free survival [PFS], time to progression [TTP], time to treatment failure [TTF], response duration, disease-free survival [DFS], and overall survival [OS]) according to the 1999 IWG criteria and the 2007 IWG criteria for patients who underwent positron emission tomography (PET) or PET-computed tomography (PET-CT).
- To evaluate pharmacodynamics (B-lymphocyte [B-cell] kinetics), overall safety, and biomarkers of CTP10 in comparison with Rituxan.

Non-inferiority Margin

The applicant proposed the non-inferiority margin of 7% based on historical studies (Marcus et al. 2005 [36] and Federico et al. 2013 [37]). In the Marcus historical study, MabThera showed 81% ORR (CR + CRu + PR) compared with CVP alone which showed a 57% ORR. In the Federico historical study, the ORR was shown as 88%. Considering the difference between these two studies, the 7% non-inferiority margin was selected.

Sample Size

Sample size was based on the primary endpoint ORR (Part 2). A sample size of 134 patients (67 patients in each treatment group) was planned to obtain 116 evaluable patients (58 patients in

each treatment group) assuming 13% drop out rate. The study was under-powered to demonstrate equivalence with respect to the primary endpoint.

Primary Endpoint

The primary endpoint was ORR (CR + CRu +PR) during the Core Study Period, as per the 1999 IWG criteria. ORR was defined as the proportion of patients with a best overall response of CR, CRu or PR. The best overall response was the best response recorded from randomization until progressive disease, start of new anticancer therapy, end of the Core Study Period or death, whichever came first. If the best overall responses of two or more assessment visits were the same, then the best overall response of the earlier assessment date was used.

Secondary Endpoint

- ORR during the Core Study Period as per 2007 IWG criteria for patients who underwent PET or PET-CT. The best overall response criteria were applied as specified in above, except for CRu. The proportion of overall responders over 8 cycles of treatment were summarized by treatment group.

- PFS defined as the time from randomization to disease progression, relapse after complete remission or death from any cause, whichever occurred first. Patients were to be censored without disease progression/relapse or death at the time of the last tumor assessment before starting another anticancer therapy.

- Duration of response defined as the time to the first documentation of relapse or progression from the first time when criteria of response (CR, CRu or PR) is met.

- OS defined as the interval between randomization and death from any.

Analysis Method

Overall response rate over 8 cycles of CVP backbone treatment was compared between CT-P10 and Rituxan. The lower bound of the 90% confidence interval for the difference between ORR of CT-P10 and US-Rituxan being greater than -7% rejects the null hypothesis in favor of noninferiority of CT-P10 to US-Rituxan.

A time-to-event analysis by the Kaplan-Meier method was performed for each of the PFS, TTP, TTF, response duration, DFS, OS, and follow-up duration endpoints in the PP population and the ITT population according to the 1999 IWG criteria and the 2007 IWG criteria for patients who underwent PET or PET-CT, whichever was applicable.

Results of Analysis

The estimated ORR in each treatment arm are summarized in the table below. The ORR difference was 5.7% (90% CI, -1.7%, 14.7%). The lower bound of the 90% CI was greater than the proposed non-inferiority margin -7%, therefore the primary objective was met for non-inferiority of ORR. However, the upper bound of the difference does not rule out superiority, which may be due to the fact that the study was underpowered.

Table 10. ORR for Study CT P10 3.3

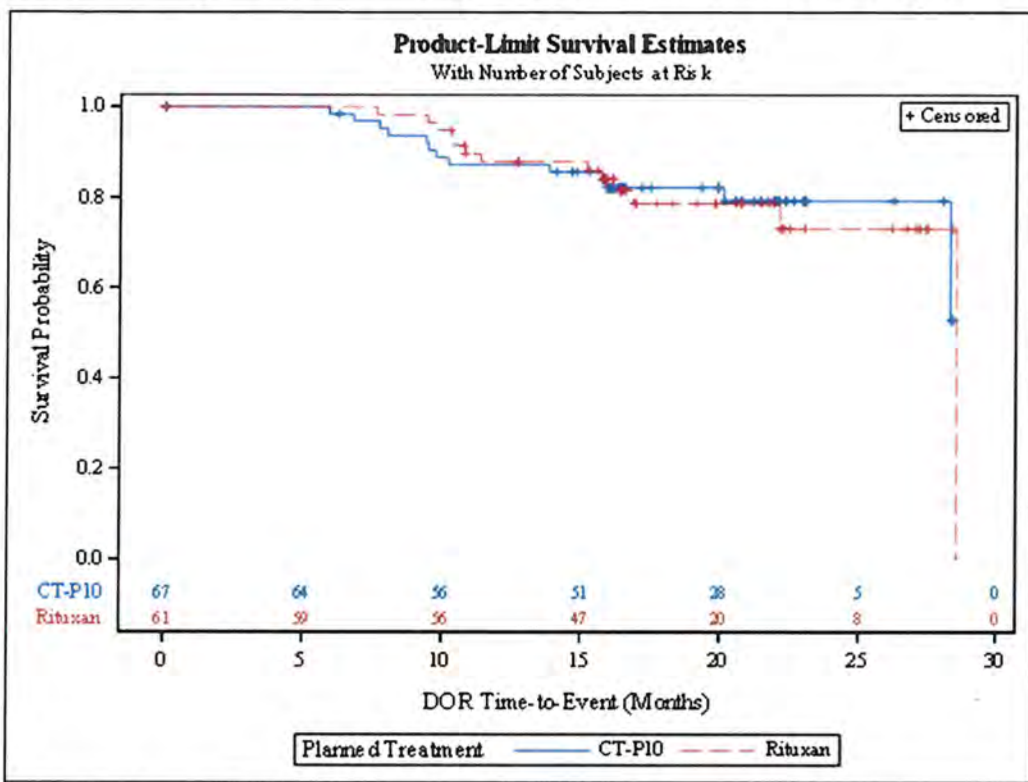
	CT-P10 (N = 70)	**US-Rituxan** (N = 70)
Overall Response	67 (95.7%)	63 (90.0%)
CR	21 (30.0%)	15 (21.4%)
Cru	6 (8.6%)	8 (11.4%)
PR	40 (57.1%)	40 (57.1%)
SD	1 (1.4%)	2 (2.9%)
PD/RD	1 (1.4%)	2 (2.9%)
Unable to Assess	0	1 (1.4%)
Missing	1 (1.4%)	2 (2.9%)
ORR difference	5.7% (90% CI, -1.7%, 14.7%)	

Source: FDA analysis

The Kaplan-Meier curves of the duration of response are shown in Figure 23. The median duration of response was not estimable (NE) in the CT-P10 arm (95% CI, 28.3, NE) vs. 28.6 months in the US-Rituxan arm (95% CI, NE, NE). The Kaplan–Meier curves do not show significant differences with respect to duration of response.

The Kaplan-Meier curves of the duration of response are shown in the following figure. The median duration of response was not estimable (NE) in the CT-P10 arm (95% CI, 28.3, NE) vs. 28.6 months in the US-Rituxan arm (95% CI, NE, NE).

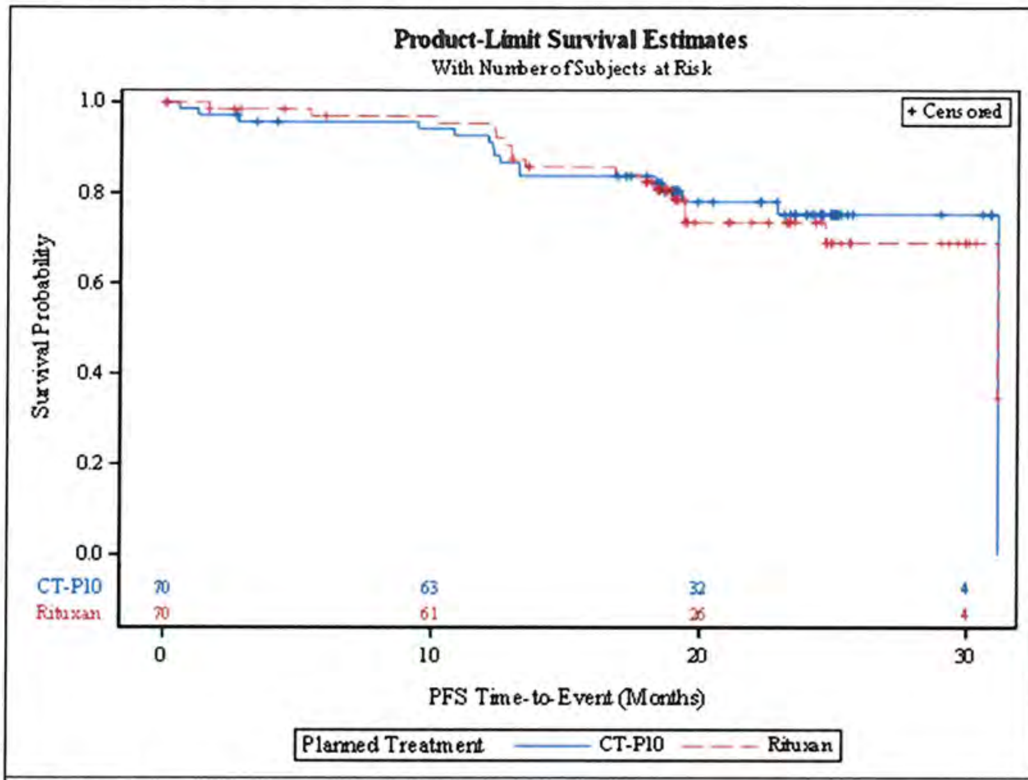
Figure 23. Kaplan-Meier Curves of Duration of Response for Study CT-P10 3.3



Source: FDA analysis

The Kaplan-Meier curves of the PFS are shown in Figure 24. The median PFS 31.2 months in the CT-P10 arm (95% CI, NE, NE) vs. 31.1 months in the US-Rituxan arm (95% CI, NE, NE). The Kaplan–Meier curves do not show significant differences with respect to progression-free survival.

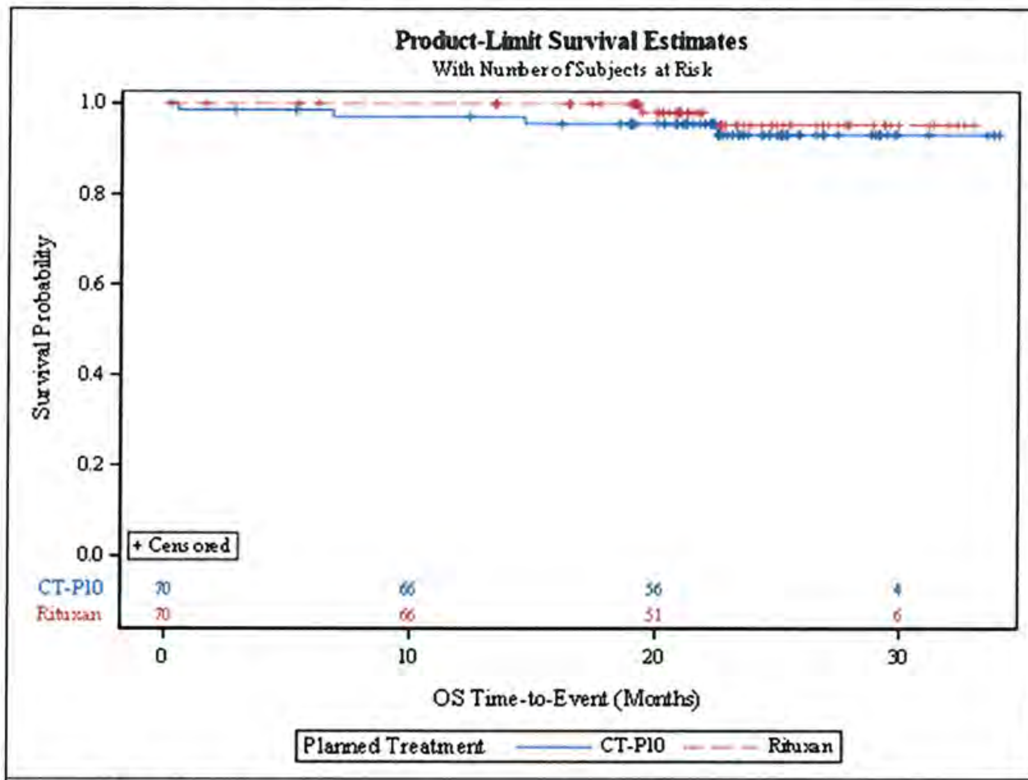
Figure 24. Kaplan-Meier Curves of PFS for Study CT-P10 3.3



Source: FDA analysis

The Kaplan-Meier curves of the OS are shown in Figure 25. The median OS was not evaluable in either of the two treatment arms. The Kaplan – Meier curves do not show significant differences with respect to overall survival.

Figure 25. Kaplan-Meier Curves of OS for Study CT-P10 3.3



Source: FDA analysis

In summary, Study 3.3 was underpowered and not adequately designed to rule out superiority of CT-P10 compared to US-Rituxan. Based on the details of Celltrion's development program, FDA would recommend an equivalence design, rather than NI, in the comparative clinical study in an oncology population to support a demonstration of no clinically meaningful differences for the sought indications. While the NI design of Study 3.3 raised uncertainty regarding this demonstration, Study 3.4 described below was designed as an equivalence study.

Study CT-P10 3.4

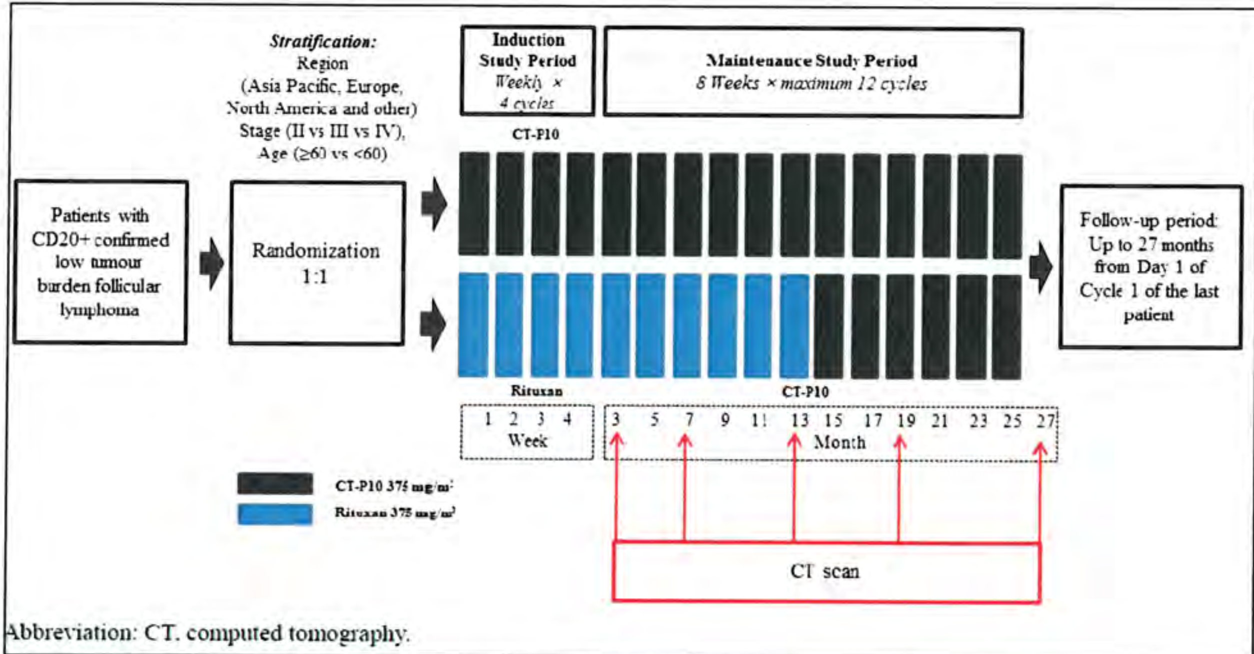
Study Design

Study CT-P10 3.4 is a randomized, parallel-group, active-controlled, double-blind study to compare clinical outcomes and safety between CT-P10 and US-Rituxan in patients with low tumor burden follicular lymphoma.

The primary objective was to evaluate whether CT-P10 is similar to US-Rituxan in terms of response to treatment as determined by the overall response rate (ORR) (complete response [CR]+unconfirmed CR [CRu] + partial response [PR]) at 7 months (prior to MC3) according to the Modified Response Criteria for Malignant Lymphoma.

The study design is shown in Figure 26.

Figure 26. Design of Study CT-P10 3.4



Abbreviation: CT, computed tomography.

Source: Figure 9-1, Clinical Study Report, Study CT-P10 3.4

The study included the following 4 periods:

1. Screening period (up to 6 weeks)
   Patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study and randomly assigned to receive the study drug (either CT-P10 or US-Rituxan) in a 1:1 ratio using a computer-generated randomization schedule that was prepared before the start of the Study. Randomization was stratified by region (Asia Pacific vs. Europe vs. North America and other), Ann Arbor stage (II vs. III vs. IV), and age (≤ 60 vs. < 60 years).

2. Induction Study Period (up to 4 weeks)
   Dose: 375 mg/m2, administered by an IV infusion, weekly for 4 weeks. The end of treatment 1 (EOT1) visit was to occur 1 week (+/- 1 day) after the last dose of study drug administration in the Induction Study Period.

   Patients were to be assessed 8 weeks (+/- 7 days) after the last dose of study drug administration in the Induction Study Period and the Investigator was to determine whether the patients qualified to continue into the Maintenance Study Period (based on assessment at the EOT2 visit).

Patients who experienced progressive disease, or their disease status was unknown, were not entered into the Maintenance Study Period and were withdrawn from the study treatment. These patients were entered into the Follow up period, provided that they had not withdrawn consent.

Patients who experienced a CR, CRu, PR, or stable disease at the EOT2 assessment qualified to continue into the Maintenance Study Period.

3. Maintenance Study Period (up to maximum of 12 cycles over 2 years)

   The first dose of study drug in the Maintenance Study Period was to be administered 8 weeks (+/- 7 days) after the last dose of study drug administration in the Induction Study Period (i.e., Day 1 of Cycle 4)

   The Maintenance Study Period was to continue for a maximum of 12 cycles over 2 years, with study drug administered at a dose of 375 mg/m2 by IV infusion every 8 weeks.

   The first year of Maintenance Period (MP1) consisted of 6 cycles of maintenance therapy (MC1 TO 6) and the second year of the Maintenance Period (MP2) consisted of 6 cycles of maintenance therapy (MC7 TO 12). After completion of MP1, once the similarity between the study drugs had been confirmed, additional CT-P10 administration was offered to all patients who had completed MP1, at the discretion of the participating investigator.

   The EOT3 visit occurred 8 weeks (+/- 7 days) after the last dose of study drug administration in the Maintenance Study Period.

   If a patient terminated study drug within 6 months from Day 1 of Cycle 1 of the Induction Study Period, the EOT3 visit occurred within 4-8 weeks (+/- 7 days) after the last dose of study drug administration in the Maintenance Study Period.

4. Follow up period (up to 27 months from Day 1 of Cycle 1 of the Induction Study Period for the last patient)

During the Follow-Up Period, patients were monitored every 6 months (+/- 2 weeks) for disease status until treatment with a new anticancer therapy or disease progression, and every 3 months (+/- 2 weeks) for survival and salvage treatment until death or study termination.

Equivalence Margin

The equivalence margin of ±17% preserved at least 77% efficacy, based on the lower bound of the 95% CI of the estimated difference in ORR of patients who received 6 doses of rituximab (88%, 162/184), and of patients in the "watch and wait" group (6%, 9/155) in Ardeshna et al (2014) [38]. The historical efficacy of rituximab based on the difference in ORR between the patients treated with rituximab and patients in the "watch and wait" group was 82%, with 95%

CI of (0.75, 0.88). Therefore, the historical treatment efficacy of rituximab for the equivalence margin was estimated as 75% conservatively and by applying a 77% preservation rate, the equivalence margin was proposed as ±17%.

Sample Size

Sample size was based on the primary endpoint, proportion of patients with a CR, CRu, or PR (the "responders") prior to MC3 (up to 7 months). A sample size of 174 patients (87 patients in each treatment group) produced a 91% statistical power for equivalence in ORR up to 7 months, based on an ORR of 88% and an equivalence margin of ±17%, using a 2-sided 90% CI approach.

The actual dropout rate and pooled ORR were assessed in a blinded manner at the DSMB meeting when the primary endpoint evaluation was available with 102 (53.7%) evaluable patients during the study. A reassessment of sample size accounting for the actual dropout rate and the observed ORR was done in a blinded manner in order to achieve an adequate statistical power for the primary endpoint (at least 80% power in the PP population). The DSMB suggested that the total sample size for this study was increased to at least 238 patients and up to 250 patients in order to achieve an adequate statistical power.

Primary Endpoint

The primary endpoint was ORR (CR+CRu+PR) prior to MC3 (at 7 months) according to the Modified Response Criteria for Malignant Lymphoma.

Secondary Endpoint

- Overall response rate (CR + CRu + PR) during the study period according to the Modified Response Criteria for Malignant Lymphoma.
- Progression-free survival, defined as the time from randomization to disease progression/relapse, or death from any cause, whichever occurred first.
- Time to progression, defined as the time from randomization to disease progression/relapse or death as a result of lymphoma, whichever occurred first.
- Overall survival, defined as the time from randomization to death from any cause.

Analysis Population

The Intent to Treat (ITT) population and per-protocol (PP) population were considered in the analysis. The ITT population was defined as all patients enrolled and randomly assigned to receive a study drug, regardless of whether or not any study drug dosing was completed. The PP population was defined as all patients who were randomly assigned and had at least one response evaluation after receiving at least one dose (full) of study drug in the Induction Study Period

without any major protocol violation or deviation that may have affected the interpretation of study results. Patients in the PP population were analyzed according to the treatment group to which they were randomized by IWRS or IVRS, and not according to what they actually received.

Analysis Method

The ORR at 7 months was compared between the CT-P10 and US-Rituxan groups for the ITT and PP populations. A point estimate and 90% CI of the difference in the proportion of responders between the 2 treatment groups were presented using an exact binomial method. If the 2-sided 90% CI for the true difference in the proportion of responders between CT-P10 and US-Rituxan was within the equivalence margin of ± 17%, then the similarity of CT-P10 to US-Rituxan with respect to response rate could be claimed for this endpoint.

Missing Data Handling Strategies

For the primary endpoint ORR, patients with missing status of ORR or ORR unable to assess were considered non-responders in the primary analysis. A tipping point analysis was performed to assess the robustness of the primary analysis findings to the missing data.

Results of Analysis

The estimated ORR in each treatment arm is summarized in the table below. The ORR difference was 1.8% (90% CI, -6.16%, 10.02%) by FDA's analysis. In both the FDA analysis and the Applicant's analysis, the entire 90% CIs lie within the equivalence margin of ± 17%.

The 90% confidence interval for the difference in ORR between CT-P10 and US-Rituxan was within the ± 17% margins. This finding supports the assertion that there are no clinically meaningful differences between the two products. Additionally, sensitivity analyses evaluating possible impacts of missing data being imputed under various assumptions also fell within the 17% margin, supporting the primary analysis conclusion.

The 90% confidence interval for the difference in ORR between CT-P10 and US-Rituxan was within the +/- 17% margins. This finding supports the assertion that there are no clinically meaningful differences between the two products. Additionally, sensitivity analyses evaluating possible impacts of missing data being imputed under various assumptions has no material impact on our conclusion.

Table 11. ORR for Study CT P10 3.4 (Central Review)

	CT-P10	**US-Rituxan**
ITT population	N = 130	N = 128
Overall Response	108 (83.1%)	104 (81.3%)
CR	36 (27.7%)	43 (33.6%)

	CT-P10	US-Rituxan
CRu	6 (4.6%)	2 (1.6%)
PR	66 (50.8%)	59 (46.1%)
SD	17 (13.1%)	18 (14.1%)
PD/RD	0	4 (3.1%)
Unable to Assess	0	1 (0.8%)
Missing	5 (3.8%)	1 (0.8%)
ORR difference [1]	1.8% (-6.16%, 10.02%)	
ORR difference [2]	1.8% (-6.43%, 10.20%)	
PP Population	N = 114	N = 120
Overall Response	99 (86.8%)	100 (83.3%)
CR	35 (30.7%)	41 (34.2%)
CRu	6 (5.3%)	2 (1.7%)
PR	58 (50.9%)	57 (47.5%)
SD	15 (13.2%)	15 (12.5%)
PD/RD	0	4 (3.3%)
Unable to Assess	0	1 (0.8%)
ORR difference [1]	3.5% (-4.49%, 11.43%)	
ORR difference [2]	3.5% (-4.56%, 11.56%)	

1. FDA analysis, confidence interval obtained using the Farrington-Manning score statistic (Chan and Zhang 1999)
2. Applicant analysis, confidence interval obtained using a different method

Sensitivity analyses were performed by using the local review of patients' response status. Similarly, in both the FDA analysis and the Applicant's analysis, the entire 90% CIs lie within the equivalence margin of ± 17%.

Table 12. ORR of Study CT P10- 3.4 (Local Review)

	CT-P10	US-Rituxan
ITT population	N = 130	N = 128
Overall Response	97 (74.6%)	100 (78.1%)
CR	31 (23.8%)	41 (32.0%)
CRu	7 (5.4%)	4 (3.1%)
PR	59 (45.4%)	55 (43.0%)
SD	27 (20.8%)	24 (18.8%)
PD/RD	1 (0.8%)	3 (2.3%)
Missing	5 (3.8%)	1 (0.8%)
ORR difference [1]	-3.5% (-12.32%, 5.31%)	
ORR difference [2]	-3.5% (-12.36%, 5.63%)	
PP Population	**N = 114**	**N = 120**
Overall Response	90 (78.9%)	96 (80.0%)

	CT-P10	US-Rituxan
CR	30 (26.3%)	40 (33.3%)
CRu	7 (6.1%)	4 (3.3%)
PR	53 (46.5%)	52 (43.3%)
SD	24 (21.1%)	21 (17.5%)
PD/RD	0	3 (2.5%)
ORR difference [1]	-1.1% (-10.12%, 7.95%)	
ORR difference [2]	-1.1% (-10.24%, 7.96%)	

1. FDA analysis, confidence interval obtained using the Farrington-Manning score statistic (Chan and Zhang 1999)
2. Applicant analysis, confidence interval obtained using a different method

The results of tipping point analyses are summarized in Table 13 and Table 14.

Table 13. Tipping Point Analysis of ORR for Study CT P10 3.4 (ITT Population, Central Review)

CT-P10	US-Rituxan		
	0	1	2
0	1.83 (-6.16, 10.02)	1.05 (-7.01, 9.08)	0.26 (-7.60, 8.31)
1	2.60 (-5.31, 10.62)	1.81 (-6.03, 9.88)	1.03 (-6.90, 9.07)
2	3.37 (-4.45, 11.39)	2.58 (-5.22, 10.62)	1.80 (-6.00, 9.66)
3	4.13 (-3.68, 12.15)	3.35 (-4.45, 11.24)	2.57 (-5.22, 10.33)
4	4.90 (-2.90, 12.89)	4.12 (-3.68, 11.90)	3.34 (-4.35, 11.01)
5	5.67 (-2.13, 13.46)	4.89 (-2.75, 12.70)	4.11 (-3.60, 11.77)

FDA analysis, confidence interval obtained using the Farrington-Manning score statistic (Chan and Zhang 1999)

Table 14. Tipping Point Analysis of ORR for Study CT-P10 3.4 (ITT Population, Local Review)

CT-P10	US-Rituxan	
	0	1
0	-3.51 (-12.32, 5.31)	-4.29 (-13.04, 4.76)
1	-2.74 (-11.50, 6.03)	-3.52 (-12.22, 5.22)
2	-1.97 (-10.83, 7.00)	2.75 (-11.40, 6.00)
3	-1.20 (-10.03, 7.54)	-1.98 (-10.83, 6.90)
4	-0.43 (-9.08, 8.31))	-1.21 (-10.03, 7.54)
5	0.34 (-8.31, 9.08)	-0.44 (-9.08, 8.31)

FDA analysis, confidence interval obtained using the Farrington-Manning score statistic (Chan and Zhang 1999)

Conclusions—Clinical Efficacy

Study CT-P10 3.3 was designed as a non-inferiority study with a margin of 7% for the primary endpoint ORR during the Core Study Period (i.e. after Cycle 8). In study CT-P10 3.3, the estimated ORR difference was 5.7% (90% CI, 14.7%) at MC3 (i.e. Up to 7 months). The lower

bound of the 90% CI was greater than the proposed non-inferiority margin, therefore the study met the primary objective for non-inferiority of ORR. However, the 90% upper bound of the difference does not rule out superiority, which may due to the fact that Study CT-P10 3.3 was under powered.

Study CT-P10 3.4 used an equivalence design for the primary endpoint of ORR with an equivalence margin of ± 17%. The estimated ORR difference 1.8% (90% CI, -6.16%, 10.02%) lies within the equivalence margin. The results of tipping point analysis showed that the analysis result was robust with respect to the missing data.

8. Safety

Executive Summary

The safety results for studies CT-P10 3.3 and 3.4 are presented below. The safety results of Study CT-P10 3.2 were also reviewed[2]. While some numerical differences were identified in all three clinical studies, it was deemed that these differences were not likely to be clinically meaningful.

Methods

The Safety Populations in studies CT-P10 3.3 and CT-P10 3.4 consisted of all subjects who received at least one (full or partial) dose of study drug.

Results

An overview of the major safety findings for Study CT-P10 3.3 and Study CT-P10 3.4 is shown in Table 15 and Table 16, respectively.

Table 15. Study CT-P10 3.3 Summary of Safety Results

	CT-P10 (N=70) n(%)	US-Rituxan (N=70) n(%)
Subjects With at Least One TEAE	63 (90.0)	60 (85.7)
Subjects With at Least One SAE	21 (30.0)	13 (18.6)
Subjects Discontinuing Study Drug due to a TEAE	7 (10.0)	5 (7.1)
Subjects With a TEAE Resulting in Death	3 (4.3)	1 (1.4)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

[2] Study 3.2 was conducted in a RA population. The applicant is not seeking licensure for non-NHL indications; therefore, FDA is not presenting the efficacy related endpoints in Study CT-P10 3.2.

Table 16. Study CT-P10 3.4 Summary of Safety Results

	CT-P10 (N=130) n(%)	US-Rituxan (N=128) n(%)
Subjects With at Least One TEAE	94 (72.3)	90 (70.3)
Subjects With at Least One SAE	7 (5.4)	3 (2.3)
Subjects Discontinuing Study Drug due to a TEAE	4 (3.1)	0 (0)
Subjects With a TEAE Resulting in Death	2 (1.5)	0 (0)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

In Study CT-P10 3.3, there were slightly more subjects in the CT-P10 treatment group who experienced SAEs. This was likely confounded by the use of CVP backbone chemotherapy, as well as differences in the baseline occurrence of bone marrow involvement of disease, as more subjects in the CT-P10 treatment group had bone marrow involvement. The numerical differences in SAEs observed in Study CT-P10 3.3 led to uncertainty regarding the demonstration of no clinically meaningful differences between CT-P10 and US-Rituxan. There was less of a difference between treatment groups in study CT-P10 3.4.

Common adverse events that occurred in ≥ 3% of subjects in either treatment group are shown in Table 17 for CT-P10 3.3 and Table 18 for CT-P10 3.4.

Table 17. Study CT-P10 3.3 Frequency of Common Adverse Events (≥3% in any group)

	CT-P10 (N=70) n(%)	US-Rituxan (N=70) n(%)
Neutropenia	28 (40.0)	20 (28.6)
Infusion related reaction	16 (22.9)	19 (27.1)
Constipation	12 (17.1)	10 (14.3)
Upper respiratory tract infection	10 (14.3)	12 (17.1)
Alopecia	10 (14.3)	6 (8.57)
Peripheral sensory neuropathy	7 (10.0)	9 (12.9)
Nausea	8 (11.4)	7 (10.0)
Diarrhea	6 (8.6)	8 (11.4)
Fatigue	6 (8.6)	8 (11.4)
Back pain	2 (2.9)	12 (17.1)
Asthenia	5 (5.7)	7 (10.0)
Arthralgia	7 (10.0)	4 (5.7)
Anemia	6 (8.6)	5 (7.1)
Urinary tract infection	5 (7.1)	6 (8.6)
Paresthesia	3 (4.3)	8 (11.4)

Nasopharyngitis	3 (4.3)	7 (10.0)
Oedema peripheral	6 (8.6)	3 (4.3)
Abdominal pain	5 (7.1)	4 (5.7)
Pyrexia	3 (4.3)	6 (8.6)
Insomnia	3 (4.3)	6 (8.6)
Pneumonia	6 (8.6)	2 (2.9)
Myalgia	6 (8.6)	2 (2.9)
Hypertension	5 (7.1)	3 (4.3)
Dizziness	4 (5.7)	4 (5.7)
Headache	4 (5.7)	4 (5.7)
Cough	3 (4.3)	5 (7.1)
Bronchitis	4 (5.7)	2 (2.9)
Influenza	2 (2.9)	4 (5.7)
Hyperglycemia	2 (2.9)	4 (5.7)
Decreased appetite	0 (0)	6 (8.6)
Thrombocytopenia	3 (4.3)	2 (2.9)
Vomiting	3 (4.3)	2 (2.9)
Oropharyngeal pain	1 (1.4)	4 (5.7)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

Table 18. Study CT-P10 3.4 Frequency of Common Adverse Events (≥3% in any group)

	CT-P10 (N=130) n(%)	US-Rituxan (N=128) n(%)
Infusion related reaction	40 (30.8)	37 (28.9)
Fatigue	9 (6.9)	12 (9.3)
Diarrhea	8 (6.2)	12 (9.3)
Upper respiratory infection	7 (5.4)	7 (5.5)
Nausea	6 (4.6)	8 (6.3)
Nasopharyngitis	5 (3.9)	5 (3.9)
Headache	4 (3.1)	6 (4.7)
Urinary tract infection	6 (4.6)	3 (2.3)
Constipation	5 (3.9)	4 (3.1)
Asthenia	3 (2.3)	6 (4.7)
Cough	3 (2.3)	6 (4.7)
Arthralgia	4 (3.1)	2 (1.6)
Neutropenia	3 (2.3)	3 (2.3)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

In study CT-P10 3.3, more subjects in the CT-P10 treatment group experienced neutropenia. However, more subjects in the CT-P10 treatment group had bone marrow involvement of disease at baseline (45 [64.3%] in the CT-P10 treatment group versus 33 [47.1%] in the US-Rituxan

group). Among the patients with TEAE of neutropenia, 18 in the CT-P10 treatment group and 7 in the US-Rituxan group had bone marrow involvement at baseline. This suggests that the observed differences in incidence of neutropenia in study CT-P10 3.3 may be attributable to differences in baseline bone marrow involvement between the treatment groups. This difference in the incidence of neutropenia between treatment groups was not reproduced in study CT-P10 3.4.

The remainder of the common adverse events experienced in both studies were not considerably different between the CT-P10 and US-Rituxan treatment groups.

Major events of special interest which are listed as Warnings and Precautions in the prescribing information for US-Rituxan include infusion reactions, infections, cardiac adverse reactions, Hepatitis B reactivation, tumor lysis syndrome, severe mucocutaneous reactions and progressive multifocal leukoencephalopathy. Infusion related reactions and infections occurred in both studies with no imbalances between treatment arms. There were several cases of cardiac adverse events in both studies and a single case each of tumor lysis syndrome and Hepatitis B reactivation in study CT-P10 3.3. There were no cases of severe mucocutaneous reactions or progressive multifocal leukoencephalopathy in either study. See Table 19 and Table 20 for the frequency of these events in studies CT-P10 3.3 and CT-P10 3.4, respectively.

Table 19. Study CT-P10 3.3 Adverse Events of Special Interest

	CT-P10 (N=70) n(%)	US-Rituxan (N=70) n(%)
Infections	31 (44.3)	32 (45.7)
Infusion related reaction	16 (22.9)	19 (27.1)
Cardiac disorders	4 (3.1)	7 (5.5)
Tumor lysis syndrome	1 (1.4)	0 (0)
Hepatitis B reactivation	0 (0)	1 (1.4)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

Table 20. Study CT-P10 3.4 Adverse Events of Special Interest

	CT-P10 (N=130) n(%)	US-Rituxan (N=128) n(%)
Infusion related reaction	40 (30.8)	37 (28.9)
Infections	35 (26.9)	27 (21.1)
Cardiac disorders	7 (5.4)	3 (2.3)
Tumor lysis syndrome	0 (0)	0 (0)
Hepatitis B reactivation	0 (0)	0 (0)

Source: FDA analysis of data from Celltrion 351(k) BLA submission

Safety Conclusion

The safety results of studies CT-P10 3.3 and CT-P10 3.4 had slight differences between the two treatment arms. In study CT-P10 3.3, more subjects in the CT-P10 treatment group experienced neutropenia. However, this was likely confounded by the number of subjects with bone marrow involvement of disease at baseline. Results from study CT-P10 3.3 may also have been confounded by the concomitant use of CVP chemotherapy. There were no differences in the incidence of neutropenia in study CT-P10 3.4.

In Study CT-P10 3.3, more subjects who received CT-P10 experienced at least one SAE and discontinued treatment due to an adverse event. There were also more deaths in the CT-P10 treatment group than in the US-Rituxan treatment group. However, the number of patients enrolled on Study CT-P10 3.3 was relatively small and there were slight differences in baseline characteristics, which limited the interpretation of the safety results.

In Study CT-P10 3.4, the overall number of subjects who experienced adverse events and the distribution of adverse events were similar in both treatment groups. The safety results of Study CT-P10 3.4 support the demonstration that there are unlikely to be clinically meaningful differences between CT-P10 and US-Rituxan.

9. Extrapolation Across Indications

The Applicant seeks licensure for three of the non-Hodgkin's lymphoma indications for which US-licensed Rituxan is currently licensed. The CT-P10 clinical program provides clinical efficacy and safety data in patients with advanced follicular lymphoma and low tumor burden follicular lymphoma, which are applicable to the three NHL indications being sought. At this time, no extrapolation of biosimilarity to additional indications is necessary.

10. Conclusion

The totality of analytical data support the determination that CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components. Although some analytical differences were observed between CT-P10 and the analyzed lots of US-licensed Rituxan, supportive studies and justifications provided by the Applicant adequately addressed these differences.

From a pharmacology/toxicology perspective, the results of the animal studies support the demonstration of biosimilarity between CT-P10 and US-licensed Rituxan.

Anti-drug antibodies were measured using appropriately validated assays in subjects with RA (Study CT-P10 3.2). The results of the Main Study Period indicate similar incidence and titers of anti-drug antibodies (ADA) for CT-P10 and US-licensed Rituxan. The immunogenicity data

from Study CT-P10 3.2 was adequate to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

The pharmacokinetic results in Study CT-P10 3.2 were similar between CT-P10 and US-licensed Rituxan, meeting pre-specified criteria of 80-125% for all endpoints.

Additional clinical studies in patients with AFL (Study CT-P10 3.3) and LTBFL (Study CT-P10 3.4), and supportive data in patients with RA (Study CT-P10 3.2) added to the totality of the data.
From a clinical and statistical perspective, there were concerns that the safety and efficacy results of clinical study CT-P10 3.3 may not have provided support of a demonstration of no clinically meaningful differences between CT-P10 and the reference product, US-licensed Rituxan, for the targeted oncology population. However, Study CT-P10 3.4 showed the 90% confidence interval for the difference in ORR between CT-P10 and the reference product was within the +/- 17% margin. The safety results from Study CT-P10 3.4 addressed the concern of potentially clinically meaningful differences between CT-P10 and US-licensed Rituxan presented by Study CT-P10 3.3. Therefore, the totality of safety and efficacy from the clinical studies support the assertion that there are no clinically meaningful differences between the two products. Results from the sensitivity analyses and subgroup analyses were consistent and agree with the primary analysis results.

In considering the totality of the evidence, the data submitted by the Applicant show that CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive compounds, and support a demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of safety, purity, and potency of the product.

FDA requests discussion at the Oncologic Drugs Advisory Committee to obtain feedback and insights whether the totality of evidence presented supports licensure of CT-P10 as a biosimilar to US-licensed Rituxan for the indications sought. This biosimilarity determination requires the following criteria to be met:

- CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components, and
- There are no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of safety, purity and potency of the product.

11. References

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