CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761088Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology
351(k) Biosimilar Review

351(k) BLA Number, SDN	BLA 761088, SDN 33 (resubmission)
Applicant	Celltrion
Submission Date	5/29/2018
Submission Type	Standard
Link to EDR	\\CDSESUB1\evsprod\BLA761088\0033
Brand (Generic) Name	Truxima (rituximab-abbs)
Dosage Form and Strength	375 mg/m^2
Route of Administration	Intravenous
Proposed Indication(s)	Non–Hodgkin's Lymphoma (NHL) TRUXIMA (rituximab-abbs) is indicated for the treatment of adult patients with: • 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 TRUXIMA 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.
Associated IND	120885 (CT-P10)
Reference Product Information	
Brand (Generic) Name	US-licensed Rituxan (rituximab)
Dosage Form and Strength	100 mg/10 mL or 500 mg/50 mL single-use vials
OCP Review Team Signers	
OCP Review Team	Sang Chung, Ph.D. Anshu Marathe, Ph.D. Olanrewaju Okusanya, Pharm.D, M.S.

1. SUMMARY

This Biological License Application (BLA) for "rituximab-abbs" (CT-P10) has been re-submitted under Section 351(k) of the Public Health Service Act (See Original Clinical Pharmacolgy review for details dated 1/19/2018 in DARRTS). The resubmission provides a response to and/or describes the corrective actions taken by the Applicant for each deficiency communicated in the Complete Response Letter (CRL) related to clinical and product quality. There were no deficiencies in the CRL related to the clinical pharmacology information; refer to the Original Clinical Pharmacolgy review for details dated 1/19/2018 in DARRTS. PK similarity between CT-P10 and US-licensed Rituxan was demonstrated in study CT-P10 3.2 in RA patients. Similar immunogencity results were observed in study CT-P10 3.2 for CT-P10 and US-licensed Rituxan.

In this resubmission, new pharmacokinetic information obtained in the comparative clinical study CT-P10 3.4 conducted in patients with low tumor burden follicular lymphoma was also included. However, the PK data from Study 3.4 were only considered as supportive; sparse PK sampling was collected (i.e., Cmax and Ctrough from the Induction or Maintenanace cycles). In study CT-P10 3.4, there were no apparent differences in Cmax and Ctrough values between CT-P10 and US-licensed Rituxan. A summary of the Cmax and Ctroughs by Cycle is shown in Table 1 in the Appendix. The PK data supports the previous assessment of PK similarity between CT-P10 and US-licensed Rituxan of the original clinical pharmacology review of this BLA.

Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II and V has reviewed the clinical pharmacology information provided in the resubmission for BLA 761088, and we recommend approval this submission from a clinical pharmacology perspective.

Appendix 1

Table 1. Summary (Mean and SD) of Serum C_{max} and C_{trough} for US-Rituxan and CT-P10 in Study CT-P10 3.4 by Cycle

PK parameter	Phase*	Cycle	CT-P10 (N=129)			US-Rituxan (n=128)		
			N	Mean	SD	N	Mean	SD
C_{max} (μg/mL)	Induction	1	129	212.473	50.63	128	217.378	56.33
		2	128	282.805	53.98	127	285.981	62.26
		3	126	327.041	70.84	126	341.591	77.95
		4	126	373.675	70.26	128	383.055	83.86
	Maintenanace	1	121	256.620	65.45	117	265.028	53.73
		2	120	239.506	65.48	116	249.862	69.02
C_{trough} (μg/mL)	Induction	1	127	64.512	24.84	127	72.936	40.39
		2	128	113.100	34.50	126	120.920	36.02
		3	126	149.331	43.53	128	161.802	43.91
		4	123	34.715	33.45	125	31.380	19.15
	Maintenanace	1	121	22.640	37.07	117	21.349	20.90
		2	119	16.974	9.57	110	18.365	10.86

(Source: FDA analysis)

SD = Standard Deviation

* Induction = weekly, 4 cycles; Maintenance = every two month, up to 12 cycles

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/s/

SANG M CHUNG
10/25/2018

OLANREWAJU OKUSANYA
10/25/2018

ANSHU MARATHE
10/25/2018

Office of Clinical Pharmacology
351(k) Biosimilar Review

351(k) BLA Number	761088
Applicant	Celltrion
Submission Date	April 28, 2017
Submission Type	Standard
Link to EDR	\\CDSESUB1\evsprod\BLA761088\0000
Brand (Generic) Name	Truxima (CT-P10)
Dosage Form and Strength	100 mg/10 mL or 500 mg/50 mL solution in a single-use vial
Route of Administration	Intravenous use
Proposed Indication(s)	• Non-Hodgkin's Lymphoma • Chronic Lymphocytic Leukemia • 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 • Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis in adult patients in combination with glucocorticoids
Associated IND	120885
Reference Product Information (U.S.-licensed)	
Brand (Generic) Name	Rituxan (Rituxumab)
Dosage Form and Strength	100 mg/10 mL or 500 mg/50 mL solution in single-use vial
OCP Review Team Signers	
OCP Review Team	Sang Chung, Ph.D. Anshu Marathe, Ph.D./Sarah J. Schrieber, Pharm.D.

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Tables and Figures

1. EXECUTIVE SUMMARY

Celltrion, Inc., the applicant, has submitted this Biologic License Application (BLA) for CT-P10 under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). CT-P10 is a proposed biosimilar to US-licensed Rituxan (BLA 10307 by Genentech), which has been approved by the Agency since 1997. The proposed indications are non-Hodgkin's lymphoma (NHL), (b) (4)

The applicant submitted pharmacokinetic (PK) similarity data that was contained within the comparative clinical study in patients with RA to support a demonstration of no clinical meaningful difference between CT-P10 and US-licensed Rituxan (Study CT-P10 3.2). Part 1 of Study CT-P10 3.2 was a randomized, controlled, double-blind, 3-arm parallel study to compare the PK CT-P10, US-licensed Rituxan and EU-approved MabThera (MabThera) in 189 patients with RA. The 90% confidence intervals (CI) for all three pairwise comparisons of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and $AUC_{0\text{-}14}$ were within the PK similarity acceptance criteria of 80 to 125% (Table 1). The results of the study established the PK similarity between CT-P10 and US-licensed Rituxan. The study also established the PK portion of the scientific bridge between CT-P10, US-licensed Rituxan, and MabThera, which supports the use of MabThera in the comparative clinical study portion within Study CT-P10 3.2.

Overall, Study CT-P10 3.2 supports a demonstration of PK similarity between CT-P10 and US-licensed Rituxan, as well as the PK portion of the scientific bridge between CT-P10, US-licensed Rituxan, and MabThera, that allows for relying on data from the study using MabThera as a comparator product for the overall biosimilarity assessment. In conclusion, the PK results support a demonstration of no clinically meaningful difference between CT-P10 and US-licensed Rituxan and add to the totality of the evidence to support a demonstration of biosimilarity of CT-P10 and US-licensed Rituxan.

The incidence of immunogenicity for CT-P10 and US-licensed Rituxan was compared in a multiple-dose, parallel-arm study in patients with RA (Study CT-P10 3.2). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. The incidence of ADA at Week 24 was 14.9% and 23.2% for CT-P10 and US-licensed Rituxan, respectively. While the development of ADAs appears to decrease exposure of the products, the impact of ADAs on PK was similar between treatment groups. No apparent impact of ADA on safety and efficacy was observed in Study CT-P10 3.2. Therefore, the data indicates that there is no increase in immunogenicity risk for CT-P10 as compared to US-licensed Rituxan, which supports the demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of CT-P10 based on demonstration of PK similarity between CT-P10 and US-licensed Rituxan in patients with RA.

Review Issue	Recommendations and Comments
Pivotal evidence of PK similarity	PK similarity was demonstrated between CT-P10 and US-licensed Rituxan in patients with RA. Additionally, the PK portion of the scientific bridge between CT-P10, US-licensed Rituxan, and EU-approved MabThera was also demonstrated. The 90% CI of the geometric mean ratio for each product pairwise comparison for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}14d}$ were within the PK similarity acceptance criteria of 80 to 125% (Table 1).
Evidence of immunogenicity comparability	The results of Study CT-P10 3.2 indicate comparable incidence of anti-drug antibodies (ADA) for CT-P10 and US-licensed Rituxan.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

CT-P10 is a proposed biosimilar to US-licensed Rituxan, which is a chimeric murine/human monoclonal immunoglobulin G1 (IgG_1) kappa antibody directed against the CD20 antigen with approximate 145 kD molecular weight. Possible mechanisms of rituximab for promoting B-cell lysis are antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and induction of apoptosis. Details on the clinical pharmacology of US-licensed Rituxan can be found in the product label (USPI).

Part 1 of Study CT-P10 3.2 conducted in 189 patients with RA demonstrated that the 90% confidence intervals (CI) for the geometric least square mean (GLSM) ratios of $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}14d}$ were within the pre-specified PK similarity acceptance criteria of 80% to 125% in the pairwise comparisons among CT-P10, US-licensed Rituxan, and MabThera (**Table 1)**.

Table 1. Summary statistical analyses for PK similarity (Study CT-P10 3.2)

Parameter	Comparison	Ratio (%) of GLSM	90% CI of Ratio (%)
Primary			

$AUC_{0\text{-}last}$	CT-P10 vs. US-Rituxan	98.5	88.7-109.5
	CT-P10 vs. MabThera	94.7	85.1-105.3
	MabThera vs. US-Rituxan	104.1	93.5-115.8
$AUC_{0\text{-}inf}$	CT-P10 vs. US-Rituxan	97.1	87.9-107.3
	CT-P10 vs. MabThera	89.4	80.8-99.0
	MabThera vs. US-Rituxan	108.6	98.1-120.2
$AUC_{0\text{-}14d}$	CT-P10 vs. US-Rituxan	98.9	90.8-107.7
	CT-P10 vs. Mabhera	89.0	81.6-97.1
	MabThera vs. US-Rituxan	111.1	101.9-121.1
Secondary			
C_{max}	CT-P10 vs. US-Rituxan	96.7	90.3-103.7
	CT-P10 vs. MabThera	89.3	83.3-95.7
	MabThera vs. US-Rituxan	108.3	101.0-116.2

Source: FDA analysis

Overall, the submitted clinical pharmacology study adequately demonstrated similarity of PK among CT-P10, US-licensed Rituxan, and MabThera in patients with RA. The PK results support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan, and add to the totality of the evidence to support a demonstration of biosimilarity of CT-P10 and US-licensed Rituxan.

The incidence of immunogenicity for CT-P10 and US-licesned Rituxan was compared in a multiple-dose, parallel-arm study in patients with RA (CT-P10 3.2). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. The incidence of ADA at Week 24 was 14.9% and 23.2% for CT-P10 and US-licensed Rituxan respectively. While the development of ADAs appears to decrease exposure of the products, the impact of ADAs on PK was similar between treatment groups. No apparent impact of ADA was observed on safety or efficacy. Therefore, the data indicates that there is no increase in immunogenicity risk for CT-P10 as compared to US-licensed Rituxan, which supports the demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

2.2 Outstanding Issues

None from the clinical pharmacology perspective.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 Describe relevant regulatory history for the review of this 351(k) BLA.

CT-P10 is a proposed biosimilar to US-licensed Rituxan. The applicant is seeking licensure for the same indications as US-licensed Rituxan, except where any of the indications are protected by either orphan designation or other exclusivity status.

3.2 Clinical Pharmacology Review Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?

The applicant conducted one comparative clinical study CT-P10 3.2 to evaluate the PK similarity and therapeutic similarity in patients with RA. An additional supportive comparative clinical study CT-P10 3.3 in patients with advanced follicular lymphoma (AFL) was also submitted (**Appendix 4.2**). These studies are summarized in **Table 2**.

Table 2. Summary of relevant clinical studies

Study	Design/objectives	Subjects	Dosing regimen
PK Similarity Study and Comparative Clinical Study (Figure 1)			
CT-P10 3.2	**Part 1: 3-way PK similairy**; double-blind, randomized, , 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of CT-P10 (n=64), US-licensed Rituxan (n=65), and EU-approved MabThera (n=60) **Part 2: Therapeutic similarity** (main study period; n=372, extension period; n=295)	Rheumatoid arthritis (RA)	Two-1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks
Supportive Clinical Study (Appendix 4.2)			
CT-P10 3.3)	Part 1 (core study period): PKevaluation; double-blind, randomized, 2-arm, active-controlled, parallel-group study designed with up to 8 cycles, compared the pharmacokinetic profiles of CT-P10 and US-licensed Rituxan (n=121) Part 2 (maintenance study period): non-inferiority in efficacy (overall response rate) (n=140 including 121 from Part 1)	Advanced follicular lymphoma (AFL)	375 mg/m^2 at Day 1 of each 21-day cycle

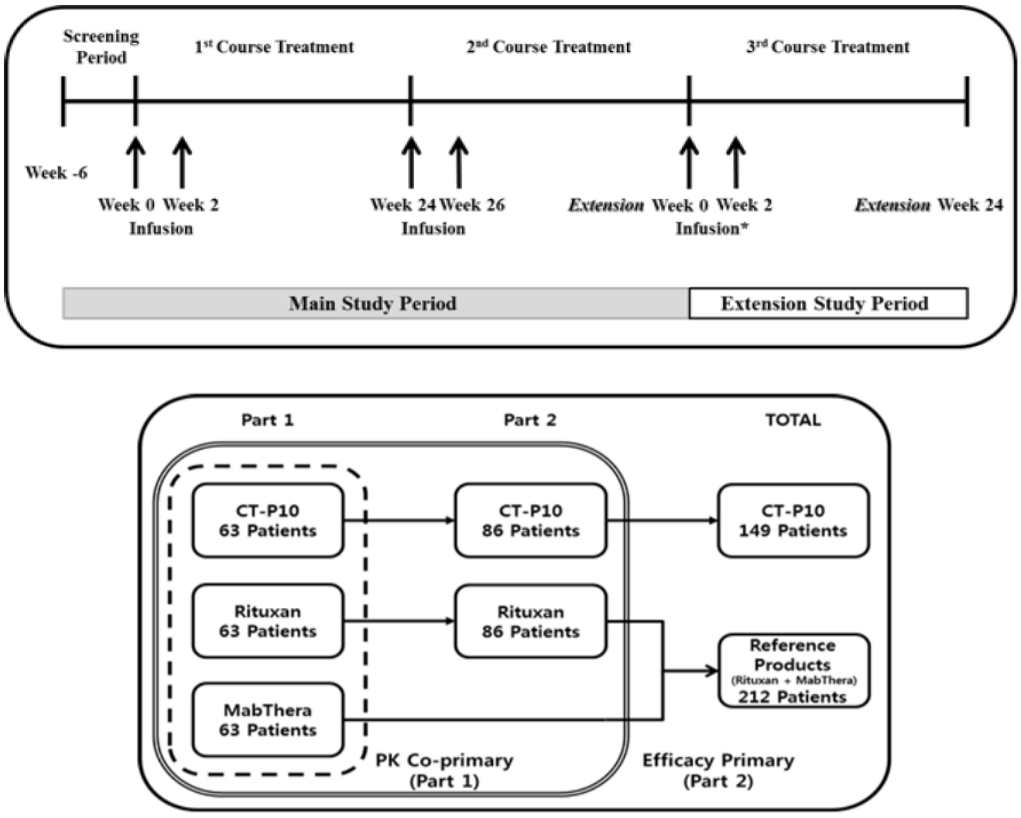

Figure 1 Schematic summary of study design (upper panel) and diagram for patients assignment for Part 1 and Part 2 (lower panel) (Study CT-P10 3.2) (Source; Figure 9-1 and 9-2, CSR CT-P10 3.2)

3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?

In Study CT-P10 3.2, the pre-specified PK similarity acceptance criteria for the primary PK parameters of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}14d}$ and secondary PK parameter of C_{max} were that the 90% CI of the geometric mean ratio should lie within 80-125%. This margin proposed by the applicant was acceptable. The following PK sampling time was adequate to characterize PK in patients with RA as it covered more than 5 times of mean terminal elimination half-life (approximately 21 days (range, 8.6-36 days)):

- On the day of each dose (Day 1) within 15 minutes prior to the beginning of infusion, and within 15 minutes and 1 hour after the end of infusion
- For patients in Part 1, additional samples were collected after 24 hours (Day 2) from the start of each infusion in the first treatment course and on Days 7, 21, 28, 56, 84 and 112.

B-cell kinetics such as B-cell depletion or recovery are known pharmacodynamics (PD) for US-Rituxan. However, B-cell counts were below the lower limit of quantification (20 cells/μL) in both Study CT-P10 3.2 (**Figure 2**). Further, the correlation between B-cell recovery and efficacy

outcomes is known to be inconsistent. Therefore, B-cell kinetic data is considered exploratory and was not used for supporting similarity assessments between CT-P10 and US-Rituxan.

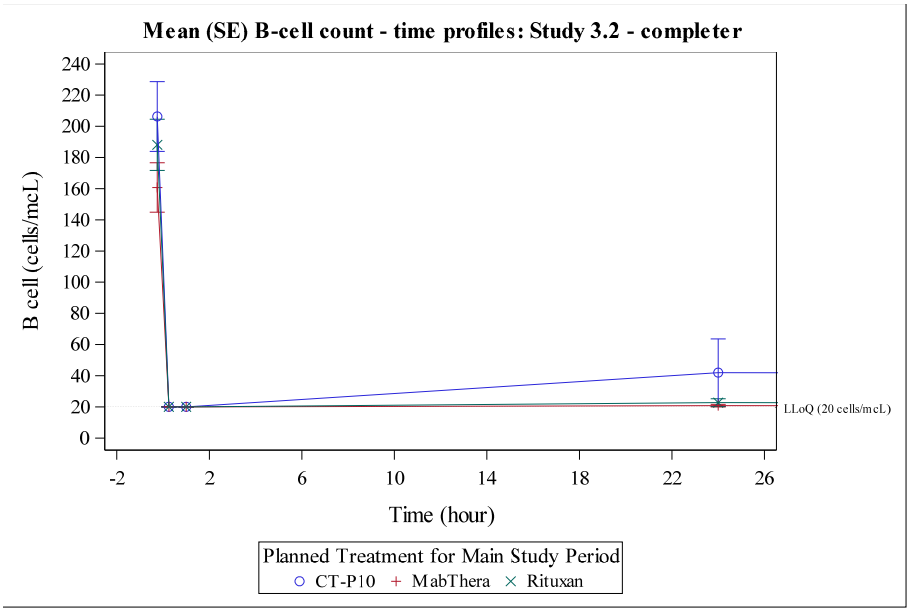

Figure 2. Mean (SE) B-cell count-time profiles from Study CT-P10 3.2 (Source; reviewer's analysis)

3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. See **Appendix 4.1** for details. Rituximab concentrations were measured in serum by a validated electrochemiluminescent (ECL) immunoassay method.

3.2.4 Is PK similarity met?

Study CT-P10 3.2 in patients with RA

Yes, PK similarity between CT-P10, US-licensed Rituxan, and EU-approved MabThera was demonstrated, where the 90% confidence intervals of geometric mean ratios of PK endpoints for each product pairwise comparison were contained within the pre-defined PK similarity acceptance criteria of 80 to 125% (**Table 1**). Also, as shown in **Figure 3**, the PK profiles of CT-P10, US-licensed Rituxan, and MabThera overlay each other. A summary of the PK parameters from Study CT-P10 3.2 is shown in **Table 3**.

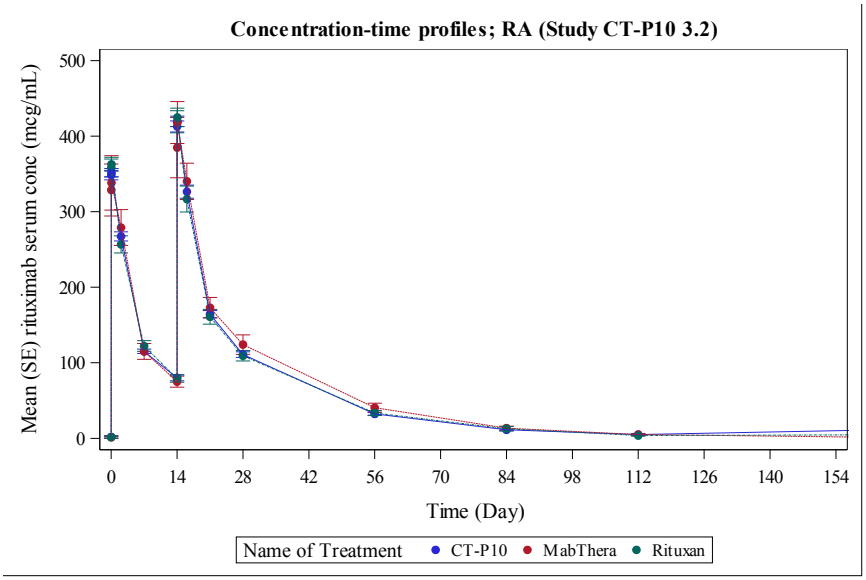

Figure 3. Mean (SE) rituximab serum concentration vs. time profile in patients with RA (Study CT-P10 3.2) (Source; reviewer's analysis)

Table 3 Summary of PK parameters in patients with RA (Study CT-P10 3.2) (Source; Table 11-12, CSR CT-P10 3.2)

Parameter (Unit)	CT-P10 (N=62)	US-Rituxan (N=63)	MabThera (N=59)
AUC_{0-inf} (h*µg/mL)			
N	62	63	59
Mean (CV%)	188400.03 (34.7)	184121.66 (35.6)	199754.50 (34.1)
AUC_{0-last} (h*µg/mL)			
N	59	62	56
Mean (CV%)	184478.20 (30.6)	187138.88 (34.1)	206484.59 (31.3)
$AUC_{0-day14}$ (h*µg/mL)			
N	62	63	59
Mean (CV%)	48726.70 (25.9)	49979.93 (28.6)	54419.65 (23.5)
C_{max} (µg/mL)			
N	62	63	59
Mean (CV%)	425.05 (22.5)	423.07 (29.3)	474.19 (21.2)
CL (mL/h)			
N	59	62	56
Mean (CV%)	11.96 (33.0)	12.56 (49.9)	10.70 (32.7)
T ½ (day)			
N	59	62	56
Mean (CV%)	15.04 (20.0)	15.19 (23.6)	15.65 (20.4)
$C_{min\ Week\ 24}$ (µg/mL)			
N	54	57	56
Mean (CV%)	0.36 (163.1)	0.45 (158.8)	0.47 (162.2)

In addition to the ANOVA analysis conducted by the reviewer (**Table 1**), statistical analysis on the primary PK endpoints was peformed using Analysis of Covariance (ANCOVA) model with treatment group as a fixed effect and gender, country (or region; EU vs. non-EU), race, prior anti-

TNF-α blocker status (intolerance case versus inadequate response), and rheumatoid factor (RF) or anti- cyclic citrullinated peptide (CCP) status (both positive versus both negative versus either RF or anti-CCP negative) as covariates by the applicant. The results of applicant's analysis also demonstrated that the 90% CIs of the geometric mean ratios for $AUC_{0-\infty}$, $AUC_{0-last,}$ and AUC_{0-14} were within the 80%-125% margin for all three comparisons (CT-P10 vs. US-Rituxan, CT-P10 vs. MabThera, and MabThera vs. US-Rituxan).

3.2.6 What is the ability of the immunogenicity assay to detect antidrug antibodies (ADA) in the presence of concentration of product in the study samples?

The electrochemiluminescence (ECL) - based immunoassay method is applied using the Meso Scale Discovery (MSD) SECTOR Imager 6000 platform, following the three-tiered ADA assay approach consisting of (i) a screening assay, (ii) specificity/confirmatory assay and (iii) titration.
The sensitivities of the binding ADA assay were <20 ng/mL for screening, specificity and titration. The lower limit of reliable detection (LLRD) was 20 ng/mL. The drug tolerance was 5 µg/mL at 20 ng/mL of ADA (screening assay) and 20 µg/mL at 250 ng/mL of ADA.

In Study CT-P10 3.2, the C_{trough} concentrations were low (< 5 µg/mL) (**Table 4**) at the ADA sampling times. Refer to Section 3.2.7 below for more information.

Refer to the immunogenicity assay review by the Office of Biological Products review for details regarding the assays.

3.2.7 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?
The sampling schedule for ADA in Study CT-P10 3.2 was appropriate to minimize interference from the presence of the product in the samples. The ADA sampling schedule was as follows: predose on Day 1, and predose on Weeks 24 and 48.

3.2.8 What is the incidence of anti-drug antibodies (ADA)? (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study.)
In Study CT-P10 3.2, a similar incidence of ADA was observed for CT-P10, US-licensed Rituxan and EU-approved MabThera (**Table 4**). Of note, the baseline immunogenicity incidence was high for each arm (**Table 4**), which may be attributed to the disease, prior treatments, and/or other factors.

Table 4 Immunogenicity results for ADA and NAb in Study CT-P10 3.2 (Source; Table 24, Integrated summary of Immunogenicity, Section 5.3.5.3)

Immunogenicity Test	Safety Population			
	CT-P10 (n=161)	**US-Rituxan (N=151)**	**MabThera (N=60)**	**US-Rituxan + MabThera (N=211)**
	n (%)			
Week 0 (Baseline)				
ADA Positive	19 (11.8)	13 (8.6)	7 (11.7)	20 (9.5)
NAb Positive (as % of ADA positive)	1 (5.3)	0	0	0
Week 24				
ADA Positive	24 (14.9)	33 (21.9)	16 (26.7)	49 (23.2)
NAb Positive (as % of ADA positive)	0	1 (3.0)	0	1 (2.0)
	Safety Population – 2nd Treatment Course in Main Study Period Subset			
	CT-P10 (n=142)	**US-Rituxan (N=138)**	**MabThera (N=58)**	**US-Rituxan + MabThera (N=196)**
	n (%)			
Week 48				
ADA Positive	7 (4.9)	13 (9.4)	5 (8.6)	18 (9.2)
NAb Positive (as % of ADA positive)	1 (14.3)	1 (7.7)	0	1 (5.6)

The data indicate that there is no increase in immunogenicity risk for CT-P10 as compared to US-licensed Rituxan, and supports the demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan. Of note, a scientific bridge was established between CT-P10, US-licensed Rituxan, and MabThera, supporting the relevance of comparative data generated using MabThera to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

3.2.9 Do the anti-drug antibodies (ADA) have neutralizing activity?

In Study CT-P10 3.2, the incidence of neutralizing antibody was low and similar between the products (**Table 4**).

3.2.10 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?

There was a trend of decrease in drug exposure in ADA positive subjects compared to ADA negative subjects. However, this impact was similar across all three treatments arms (**Figure 4**). No apparent impact of ADA on efficacy or safety endpoints was observed from Study CT-P10 3.2.

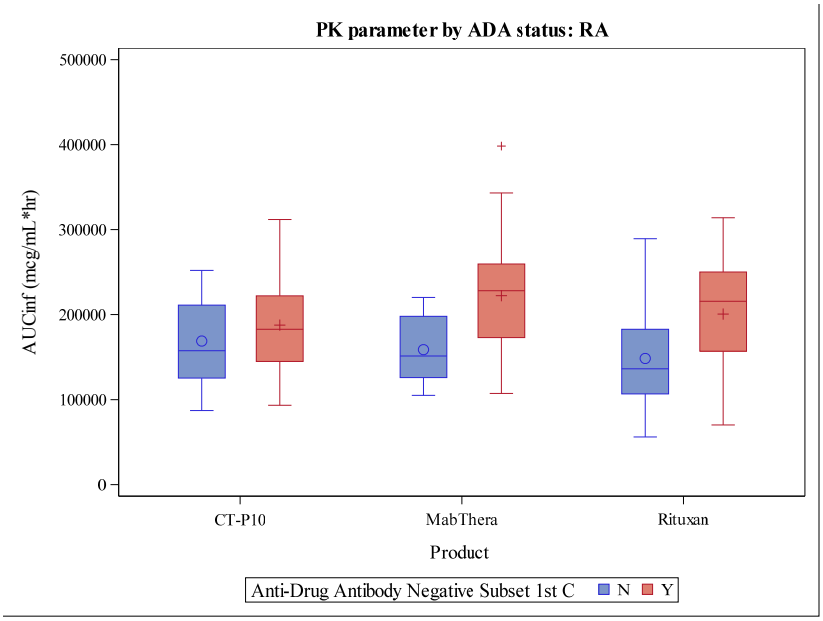

Figure 4 Box plot for $AUC_{0\text{-}inf}$ by ADA status (Y indicates ADA negative and N indicates ADA positive) among products (CT-P10, Rituxima or MabThera) (Study CT-P10 3.2) (Source; reviewer's analysis)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetics

4.1.1.1 How are the concentrations of the pharmacologically active moieties (parent and/or any relevant catabolites) measured in the plasma and other matrices in the clinical pharmacology studies?

Serum CT-P10 and rituximab concentrations were measured using a validated electrochemicluminescent (ECL) immunoassay. The method for the quantification of CT-P10, US-licensed Rituxan and EU-approved MabThera in human serum was validated at (b) (4) Laboratories (Original validation report: GOX2, addendum; GOX3, 4, 6, 7, 10, 11, 12 and 15). A summary of the ELISA assay validation for CT-P10 and EU-approved MabThera is show in **Table 5**.

In brief, procedures are as follows:

- Following a 1:25 dilution in assay buffer containing 3% BSA, human serum samples containing CT-P10 were incubated together with biotinylated rat anti-rituximab antibody (biotin) and ruthenium-labeled rat anti-rituximab antibody (TAG) and an antibody complex bridge is formed.
- When the samples are transferred to a streptavidin-coated MSD plate, the biotin portion of the complex binds to the plate. A washing step removes any unbound material

- After the addition of read buffer containing tripropylamine, the plates are read on an MSD Sector Imager 6000. The voltage applied by the reader triggers the ruthenium to produce a chemiluminescent signal which is directly proportional to the concentration of CT-P10.

A summary of the assay validation for CT-P10, and EU-approved MabThera is shown in **Table 5**, and they met acceptance criteria.

The method was modified for Study CT-P10 3.2 by the addition of mouse IgG to the minimum required diluent (MRD). The modification was introduced as the concentrations were above the LLOQ (20 ng/mL) at baseline for some subjects in a preliminary PK study It was concluded that human anti-murine antibody binding to the rat anti-rituximab detection antibody was the root cause the false positive at baseline in that preliminary PK study. The partial validation conducted for CT-P10 and US-licensed Rituxan was reviewed and deemed sufficient to support the Study CT-P10 3.2.

Table 5 Method Performance during Validation

Drug Product	**CT-P10**	**MabThera**
MRD	1:25 in assay buffer	
Validated QCs	LLOQ: 20 ng/mL, LQC: 30, or 60 ng/mL, MQC: 800 ng/mL, HQC: 7000 ng/mL, ULOQ: 10000 ng/mL	
Precision (%CV) Standards Conc. (excluding anchor points) 20.0 to 10,000 ng/mL Inter-assay (%)	0.7 to 4.3 [1-3]	
LLOQ	9.1[1]	10.4[2]
LOQ	4.74-9.31[1-3]	8.6[2]
MQC	4.1-8.7[1-3]	5.8[2]
HQC	4.1-5.7[1-3]	5.8[2]
ULOQ	4.3[1]	7.0[2]
Accuracy (%RE) Standards Conc. (excluding anchor points) 20.0 to 10,000 ng/mL Inter-assay (%)	-3.3 to 2.9 [1-3]	
LLOQ	-17.0[1]	-0.1[2]
LOQ	-13.9-2.2[1-3]	1.43[2]
MQC	-10.8 - -4.6[1-3]	-0.6[2]
HQC	-3.7- -0.84.1-5.7[1-3]	3.1[2]
ULOQ	-4.71[1]	4.4[2]
Stability (% difference) Stability Accuracy (LQC/HQC) at 2–8°C, 24 hrs at room temperature (RT), 24 hr	demonstrated [2]	demonstrated [2]
Long-term Matrix Stability (LQC/HQC) at -80°C, 46 days	demonstrated [1]	demonstrated [1]
Long-term Matrix Stability Accuracy (LQC/HQC) at -25°C±5°C, 555 days for CT-P10, 545 days for MabThera at -80°C±10°C, 1132 days for CT-P10, 1251 days for MabThera	demonstrated [4]	demonstrated [4]
Whole Blood Stability (LQC/HQC) RT or 2-8 °C for 2 hrs and centrifuged at RT or at 2-8 °C	demonstrated [3]	demonstrated [3]
Specificity & Selectivity Passed unspiked sample below LLOQ NHS/RA/NHL serum	Validated [1-2]	

Passed spiked sample at LQC within 20% Recovery NHS/RA/NHL serum	validated [1-2]	Validated [1-2]
Hemolyzed and lipemic samples (% Difference at LQC/HQC) Hemolysis (5% serum) Lipemia	Validated [1-2]	
Concomitant medications interference (% Difference at LLOQ/ULOQ) 500 ng/mL methotrexate 200 ng/mL dexamethasone 3.50 µg/mL cisplatin 150 µg/mL cyclophosphamide 3.00 µg/mL vincristine 1.80 µg/mL prednisone 3.22 µg/mL cytarabine ocfosfate 300 ng/mL folic acid	No significant interference shown [2]	
Dilutional Linearity (Up to 1:10,000 dilution) Precision (% CV) % Difference from the nominal concentration Hook effect	 ≤ 2.2 [1] ≤ 4.8 [1] Observed > 20,000 ng/mL [1]	 ≤ 6.4 [2] ≤ 6.9 [2] Observed > 50,000 ng/mL [2]

Sources: [1] GOX2, [2] GOX4, [3] GOX6, or [4] GOX3 indicates corresponding validation reports
% CV: Percent coefficient of variation, % RE: Percent relative error, HQC: High quality control (7,000 ng/mL), hr: Hour, LLOQ: Lower limit of quantification (20.0 ng/mL), LQC: Low quality control (30.0 ng/mL or 60.0 ng/mL), MQC: Medium quality control (800 ng/mL), MRD: Minimum required dilution, NHL: Non-Hodgkin's lymphoma, NHS: Normal healthy subjects, RA: Rheumatoid arthritis, RT: Room temperature, ULOQ: Upper limit of quantification (10,000 ng/mL)

4.2 Clinical Pharmacology-Related Results for CT-P10 and US-licensed Rituxan in Study CT-P10 3.3

In the comparative clinical Study CT-P10 3.3, rituximab trough serum concentrations (C_{trough}) and maximum concentrations (C_{max}) were collected at predose and postdose, respectively, on Day 1 of Cycles 1 – 8 in the Core Study Period in order to describe the PK of CT-P10 and US-licensed Rituxan. A full PK profile was also characterized in Cycle 4.

Study 20120265 was designed with two parts. Patients with advanced follicular lymphoma (AFL) received CT-P10 and US-licensed Rituxan following 375 mg/m^2 at Day 1 of each 21-day cycle. The Core Study Period was a double-blind, randomized (1:1), 2-arm, active-controlled, parallel-group study designed with up to 8 cycles to compared the pharmacokinetic profiles of CT-P10 and

US-licensed Rituxan (n=121). The maintenance study period was designed to evaluate non-inferiority (NI) in efficacy (overall response rate) (n=140 including 121 from the Core Study Period). Refer to **Table 2** and **Figure 5** for more details on the study design.

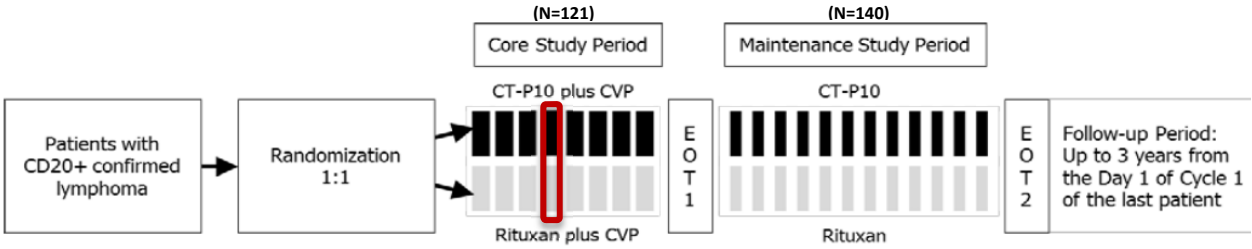

Figure 5 Schematic summary of study design (Study CT-P10 3.3) (red square indicates cycle with PK assessment) (Source; Figure 9-1, CSR CT-P10 3.3)

The PK sampling times were as follows and were collected only during the Core Study Period:

- Cycles 1 – 8 during the Core Study Period: Predose, end of infusion (within 15 min of end of infusion), and 1 hour after the end of infusion
- Cycle 4 during the Core Study Period: Additional samples were collected after 24 (Day 2), 168 (Day 8), 336 (Day 15) and 504 (Day 22) hours after the end the infusion
- End of Treatment Visit 1 (EOT1)

A summary of the mean PK paramters following dosing in Cycle 4 are presented in **Table 6**. Exposures (AUC_{tau} and C_{max}) and and inter-subject variability were comparable to that observed for US-licensed Rituxan following multiple dosing (Cycle 4, **Table 6**). The rituximab C_{trough} and C_{max} data demonstrate that apparent steady-state may be reached during Cycle 4 (**Table 7**).

Table 6 Summary of PK parameters from Cycle 4 in patients with AFL (Souce: modified from Table 14.2.1.5 or Table 11-10, CSR of Study CT-P10 3.3)

Parameter (Unit)	**CT-P10 (N=59)**	**US-Rituxan (N=62)**
AUC_{tau} (h*µg/mL)		
N	55	58
Mean (CV)	55637.53 (30.9)	60336.20 (32.4)
C_{max} (µg/mL)		
N		
Mean (CV)	271.13 (22.9)	273.05 (24.4
$T_{1/2}$ (hour)		
N	48	47
Mean (CV)	279.39 (30.3)	293.70 (22.5)
CL (L/day)		
N	55	58
Mean (CV)	0.42 (131.1)	0.33 (82.8)

Table 7 Mean (CV%) of rituximab C_{max} and $C_{trought}$ at Core Cycles 1 to 8 (Source; Table 11-11, CSR CT-P10 3.3)

Parameter (Unit)		CT-P10		US-Rituxan
Core Cycle #				
C_{trough} (µg/mL)				
Cycle 1	n=59	20.248 (199.7)	n=61	28.400 (166.4)
Cycle 2	n=57	31.312 (59.7)	n=59	43.056 (93.5)
Cycle 3	n=55	50.593 (71.7)	n=58	60.843 (80.4)
Cycle 4	n=55	60.395 (44.9)	n=58	64.256 (49.5)
Cycle 5	n=53	73.223 (46.0)	n=58	68.893 (57.8)
Cycle 6	n=52	89.471 (67.5)	n=57	94.708 (64.8)
Cycle 7	n=52	82.795 (36.3)	n=57	101.799 (62.4)
Cycle 8	n=52	106.435 (52.8)	n=56	95.523 (48.5)
C_{max} (µg/mL)				
Cycle 1	n=59	173.67 (40.8)	n=62	209.75 (21.8)
Cycle 2	n=58	206.27 (32.5)	n=60	225.94 (31.9)
Cycle 3	n=56	228.94 (30.3)	n=58	248.80 (29.8)
Cycle 4	n=55	271.13 (22.9)	n=58	273.05 (24.4)
Cycle 5	n=53	271.09 (28.3)	n=58	284.00 (26.5)
Cycle 6	n=53	285.25 (26.0)	n=58	303.79 (20.8)
Cycle 7	n=52	289.31 (26.7)	n=57	309.11 (25.5)
Cycle 8	n=52	294.11 (27.6)	n=56	300.45 (26.1)

B-cell counts were evaluated in this study and were below the lower limit of quantification (20 cells/µL) (**Figure 5**). The findings and conclusions are similar to those made for Study CT-P10 3.2 in patients with RA (see **Section 3.2.2**).

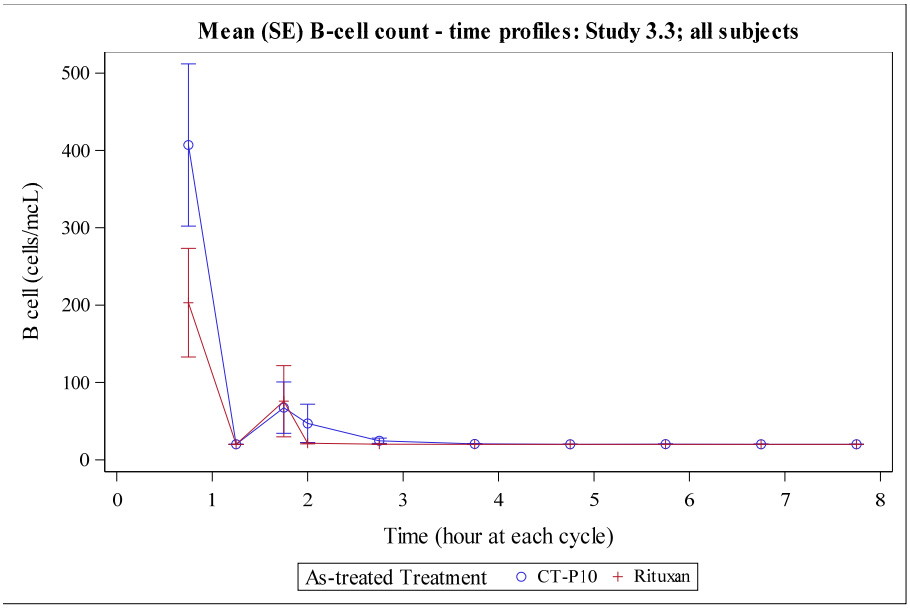

Figure 5. Mean (SE) B-cell count-time profiles from Study CT-P10 3.3 (Source: Reviewer's analysis)

Regarding immunogenicity, the threshold for drug interference at the low positive control (20.0 ng/mL) was 5 µg/mL (see **Section 3.2.6**). Drug concentration were high at the ADA sampling times (**Table 7**), and there may be false negative potential for the assessment of immunogenicity impact on the clinical endpoints due to the drug interference. Therefore, immunogenicity data are not reported for this study. Note, sampling times were as follows:

- Baseline (prior to Cycle 1 dosing in the Core Study Period)
- Core Study Period Cycle 4
- End of Core Study period at EOT1 Visit
- Maintenance Study Period Cycles 3, 6 and 9
- EOT2 visit for patients who enter the Maintenance Study Period.

Refer to the immunogenicity assay review by the Office of Biological Products review for details regarding the assays and the Division of Hematology Products review regarding clinical concerns.

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/s/

SANG M CHUNG
01/19/2018

SARAH J SCHRIEBER
01/19/2018

ANSHU MARATHE
01/19/2018