CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761088Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	31 October 2018
From	Nicole Gormley, MD and Vishal Bhatnagar, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761088
Applicant	Celltrion, Inc.
Date of Submission Receipt	29 May 2018
BSUFA Goal Date	29 Nov 2018
Nonproprietary Name	CT-P10 (also referred to as Truxima by the Applicant), rituximab-abbs*
Dosage forms / Strength	Injection: 100 mg/10 mL (10 mg/ml) and 500 mg/ 50 mL (10 mg/ml) solution in single-use vials
Proposed Indication(s)	Adult patients with Non-Hodgkin's Lymphoma (NHL) o Relapsed or refractory, low grade or follicular, CD20-positive B- cell NHL as a single agent. o Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy. o Non-progressing (including stable disease), low-grade, CD20- positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
Recommended:	Approval

* For purposes of this review, the proposed product is referred to by the Applicant's descriptor CT-P10 which was the name used to refer to this product during development. The proposed proprietary name (Truxima) and the proposed nonproprietary name (rituximab-abbs) are only conditionally accepted for this product until the application is approved.

Material Reviewed/Review Team Consulted	**Reviewer**
Clinical and Stats Review, Division of Hematology Products	Rachel Ershler, MD, Xin Gao, PhD
Division of Hematology and Oncology Toxicology	Michael Manning, PhD; Christopher Sheth, PhD
Office of Biotechnology Products	Haoheng Yan, MD, PhD; Nina Brahme, PhD, MPH; Bazarragchaa Damdinsuren, MD, PhD; Christopher Downey, PhD
Office of Product Quality, Office of Process and Facilities, Division of Inspectional Assessment	Thuy Nguyen, MPH; Zhihao Peter Qiu, PhD
Office of Product Quality, Office of Process and Facilities, Division of Microbiology	Candace Gomez-Broughton, PhD; Reyes Candau-Chacon, PhD

Assessment	
Clinical Pharmacology Review, Office of Clinical Pharmacology	Sang Ching, Ph.D.; Anshu Marathe, Ph.D.; Olanrewaju Okusanya, Pharm.D, M.S..
Office of Scientific Investigations/Division of Clinical Compliance Evaluation	Min Lu, MD, MPH; Janice Pohlman, MD, MPH; Kassa Ayalew MD, MPH
Cross-Discipline Team Leader Review dated 02/28/2018*	Nicole Gormley, MD

*** This review will primarily discuss the responses to the CR deficiencies identified during the initial review. Please refer to the CDTL review from the initial submission for further details of items not covered in this review.**

1. Introduction

On April 28, 2017, Celltrion, Inc. (Applicant) submitted BLA 761088 for CT-P10 as a proposed biosimilar product to US-licensed Rituxan (rituximab). BLA 761088 was submitted for the purpose of licensure of CT-P10 under section 351(k) of the Public Health Service Act. The proposed indications for CT-P10 in this original submission were treatment of adult patients with:

- 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.

(b) (4)

These indications are approved for US-licensed Rituxan (henceforth referred to as either "Rituxan" or "US-licensed Rituxan"), (b) (4)

The Application received a complete response on February 28, 2018 because of deficiencies identified during the facilities inspections, clinical deficiencies, and product quality deficiencies.

On May 29, 2018, Celltrion, Inc. (Applicant) re-submitted BLA 761088 for CT-P10 as a proposed biosimilar product to US-licensed Rituxan (rituximab). The proposed indications sought for this resubmission are treatment of adult patients with:

- Non-Hodgkin's Lymphoma
  - Relapsed or refractory, low grade or follicular, CD20-positive B- cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product 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.

2. Background

Source: Derived in part from the reviews by Drs. Ershler and Manning

Rituxan is a chimeric murine/human monoclonal antibody that binds to the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. After binding to CD20 on the cell surface, Rituxan can mediate B cell lysis, possibly through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and/or direct induction of apoptosis. The Applicant conducted an analytical similarity assessment of CT-P10 and Rituxan, that included studies for cell-based CD20 binding affinity, ADCC, ADCP, CDC, and apoptosis and studies that measured FcγR binding affinities, FcRn binding affinity, and C1q binding affinity.

The regulatory history pertaining to the development of CT-P10 is detailed below.

- March 19, 2014: BPD Type 2 Meeting (PIND 120885) to discuss development of CT-P10 as a proposed biosimilar to US-licensed Rituxan.
- July 13, 2015: BPD Type 2 Meeting (IND 120885) to discuss the proposed development program for supporting licensure of CT-P10 as a biosimilar to US-licensed Rituxan, as well as to obtain FDA feedback on ongoing Study CT-P10 3.3 and the proposed design of the CT-P10 3.2 extension.
- February 12, 2016: BPD Type 2 Meeting (IND 120885) to discuss the proposed development program for supporting licensure of CT-P10 as a biosimilar in the US.
- January 17, 2017: BPD Type 3 Meeting (IND 120885) to obtain Agency feedback regarding the similarity between CT-P10 and the reference product based on a comprehensive analytical data package and to reach agreement on the CMC and analytical requirements including the proposed comparability program, specifications,

process validation studies, and stability testing program, in preparation for submission of the BLA.

- January 17, 2017: BPD Type 2 Meeting (IND 120885) to obtain Agency concurrence and feedback on their proposed clinical development program with the data generated to date for the licensure of the biosimilar product CT-P10 in the US under section 351(k) of the Public Health Service (PHS) Act.
- April 26, 2017: BPD Type 4 Meeting (IND 120885) to obtain agreement with FDA on format and the content of an application for CT-P10 to be submitted under section 351(k) of the PHS Act.
- April 28, 2017: BLA 761088 was submitted to FDA.
- February 28, 2018: Complete Response (CR) Letter issued by the FDA.
- April 16, 2018: BPD Type 1 Meeting (IND 120885) to discuss the issues and recommendations identified in the CR letter and obtain agreement on the plan for resubmission.
- May 29, 2018: FDA received the resubmission for BLA 761088.
- October 10, 2018: An Oncologic Drug Advisory Committee Meeting was held to discuss BLA 761088.

CT-P10 was approved in South Korea in November 2016, and in the EU in February 2017.

The Applicant conducted a stepwise biosimilar development program intended to demonstrate that CT-P10 is highly similar to Rituxan notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of safety, purity, or potency. The biosimilar development program consists of an analytical similarity assessment and comparative nonclinical and clinical studies.

3. CMC/Device

Source: Derived in part from the OBP Review by Drs. Yan, Brahme, Damdinsuren, Nguyen, Qiu, and Downey.

CT-P10 is produced in genetically engineered CHO (b) (4) cells. The drug product is manufactured to the same concentration, formulation, and presentation as U.S.-licensed Rituxan. CT-P10 is a sterile, preservative-free, colorless to pale yellow, clear to opalescent solution for intravenous infusion and supplied in single-dose vials containing CT-P10 (10 mg/ml) at 100 mg/10 mL or 500 mg/50 mL.

The Office of Pharmaceutical Quality (OPQ), CDER, reviewed the data submitted in the BLA resubmission in response to the product quality deficiencies identified in the CR letter. There were no deficiencies related to analytical similarity and no new analytical similarity data were included in the resubmission. OPQ deemed that the data submitted in this Biologics License Application adequately support the conclusion that the manufacture of CT-P10 is well controlled and leads to a product that is pure and potent. OPQ concluded that all previously identified product quality CR deficiencies were adequately addressed. Therefore, OPQ recommended that CT-P10 be approved for human use under the conditions specified in the package insert.

OBP concluded the immunogenicity assay was adequate for the immunogenicity assessment for Study CT-P10 3.2 (see Section 5 Clinical Pharmacology/Biopharmaceutics). Refer to the OBP Immunogenicity Assay Review for BLA 761088 dated January 17, 2018 for additional details.

Per Division of Inspectional Assessment (DIA)/OPF/OPQ, all manufacturing, packaging, and testing sites listed in the BLA resubmission are recommended for approval from a facilities assessment standpoint. During the previous review cycle, a pre-license inspection of the drug substance and drug product manufacturing facility could not be conducted due to Official Action Indicated (OAI) status associated with a Warning Letter (WL 320-18-28) issued to the firm based on a post-approval inspection for (b) (4) and a GMP surveillance inspection. During the previous review cycle, DIA/OPF/OPQ recommended a withhold status and that a Complete Response be issued to Celltrion. During this review cycle, a pre-license inspection was conducted. The inspection was classified as Voluntary Action Indicated (VAI). The firm adequately addressed the FDA-483, Inspectional Observations. The application was recommended for approval from a DIA standpoint.

The Division of Microbiology Assessment (DMA)/ OPF/OPQ recommended approval from a sterility assurance and microbiology product quality perspective. The Applicant adequately addressed the deficiencies listed in the CR letter. Refer to the DMA review for further details.

From an analytical similarity perspective, OBP/OPQ determined that the analytical similarity data as presented in the original BLA was acceptable to support the conclusion that CT-P10 is highly similar to U.S.-licensed Rituxan. Refer to the CMC Executive Summary for BLA 761088 dated February 28, 2018 for additional details.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology/Toxicology Review by Drs. Manning and Sheth

No additional pharmacology/toxicology information was submitted with this re-submission.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical Pharmacology Review by Drs. Chung, Marathe, and Okusanya.

There were no deficiencies in the CR letter related to the clinical pharmacology information; refer to the Clinical Pharmacology review for BLA 761088 dated January 19, 2018 for additional details. The pharmacokinetic (PK) similarity between CT-P10 and US-licensed Rituxan was demonstrated in study CT-P10 3.2, conducted in patients with rheumatoid arthritis. Similar immunogenicity 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., C_{max} and C_{trough} from the Induction or Maintenance cycles). In study CT-P10 3.4, there were no apparent differences in C_{max} and C_{trough} values between CT-P10 and US-licensed Rituxan. The PK data from Study CT-P10 3.4 supports the previous assessment of PK similarity between CT-P10 and US-licensed Rituxan

The Office of Clinical Pharmacology recommends approval of CT-P10.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Derived in part from the DHP Clinical and Statistical Review by Drs. Ershler, Gao, Shen, and Gwise; and previous clinical and statistical reviews from the original submission.

The Applicant submitted two clinical studies that compared CT-P10 to US-licensed Rituxan in the oncology setting:

- Study CT-P10 3.3: Randomized, double-blind, active-controlled, parallel-group study in patients with advanced follicular lymphoma.
- Study CT-P10 3.4: Randomized, double-blind, active controlled, parallel-group study in patients with low tumor burden follicular lymphoma.

Table 1. Studies in Hematologic Indications

Protocol Number	Study Design	Study Population	Study Objectives	Study Drugs and Dosage	# Subjects Completed	Study Sites	Status
CT-P10 3.3	Randomized, double-blind, active-controlled, parallel-group	Advanced follicular lymphoma	Non-inferiority based on ORR over 24 weeks	CT-P10 US-Rituxan® 375 mg/m² IV	140 CT-P10: 70 US-Rituxan®: 70	64 sites in Europe, Africa, Asia, Latin America	Ongoing Final CSR 4Q/2019
CT-P10 3.4	Randomized, double-blind, active-controlled, parallel-group	Low tumor burden follicular lymphoma	ORR at 7 months	CT-P10 US-Rituxan® 375 mg/m² IV	258 CT-P10: 130 US-Rituxan®: 128	153 sites in Europe, Asia, Latin America, North America	Ongoing Final CSR 2Q/2020

Source: DHP Clinical Review (ORR: overall response rate; CSR: clinical study report)

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. The estimated 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, therefore the study met the primary objective for noninferiority. However, the study was not designed to demonstrate equivalence. Inference about equivalence would be post-hoc and likely underpowered in this study.

From the DHP clinical and statistical perspective, there were concerns that the results of the clinical study CT-P10 3.3 alone may not provide sufficient support of a demonstration of no clinically meaningful differences between CT-P10 and the reference product Rituxan for the targeted oncology population. Per the statistical reviewer, in regards to study 3.3: "Several major issues with study CT-P10 3.3 were identified during the review. First, the Agency considers that an equivalence design is generally more appropriate than a non-inferiority design to demonstrate that there are no clinically meaningful differences for this patient population. Second, study CT-P10 3.3 is designed to demonstrate non-inferiority only, and it is likely underpowered to demonstrate equivalence of CT-P10 vs. US-Rituxan. Lastly, the sensitivity of the advanced follicular lymphoma population to detect differences between products could be influenced by the presence of concurrent background chemotherapy."

Study CT-P10 3.4 used an equivalence design for the primary endpoint of ORR with equivalence margins of ±17%. The estimated ORR difference of 1.8% (90% CI, -6.16%, 10.02%) lies within the equivalence margins. Therefore, the study demonstrated the equivalence of CT-P10 vs. US-Rituxan from a statistical standpoint. The FDA statistical reviewer used more than one method to obtain confidence limits, which all were comparable to the Applicant's analysis.

Table 2. Study CT-P10 3.4: ORR Based on 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)
CRu	6 (4.6)	2 (1.6)
PR	66 (50.8)	59 (46.1)
SD	17 (13.1)	18 (14.1)
PD/RD	0 (0)	4 (3.1)
Unable to Assess	0 (0)	1 (0.8)
Missing	5 (3.8)	1 (0.8)
ORR difference [1]	1.8% (-8.31%, 12.15%)	
ORR difference [2]	1.8% (-6.16%, 10.02%)	
ORR difference [3]	1.8% (-6.43%, 10.20%)	

1. FDA statistical reviewer analysis, confidence limits obtained by inverting two separate one-sided exact tests (Santner and Snell 1980) using the unstandardized risk difference
2. FDA statistical reviewer analysis, confidence limits obtained by Farrington-Manning score statistic (Chan and Zhang 1999)
3. Applicant's analysis
Source: FDA Statistical Reviewer

The FDA statistical reviewer also performed sensitivity analyses evaluating the possible impacts of missing data from CT-P10 3.4. Even in "worst case" scenarios for missing data, the equivalence margin was between ±17%. These analyses support the conclusion that there are

no clinically meaningful differences from a clinical perspective between CT-P10 and US-Rituxan in the indications sought for licensure in the current submission.

8. Safety

Source: Derived from the DHP Clinical Review by Dr. Ershler.

The Applicant is seeking licensure of CT-P10 for three NHL indications approved for US-Rituxan. A detailed analysis of safety outcomes was conducted by the DHP review team using data from studies CT-P10 3.3 and CT-P10 3.4.

Study CT-P10 3.3

The Safety Analysis set consisted of 140 subjects with advanced follicular lymphoma who received at least 1 dose of CT-P10 (n=70) or Rituxan (n=70). There were more subjects with Grade 3 and higher adverse events and who had at least one serious adverse event in the CT-P10 treatment group. There were three deaths in the CT-P10 group and one death in the Rituxan group. The most common adverse events in patients with advanced follicular lymphoma were neutropenia, infusion-related reactions, constipation and upper respiratory infections. In Study CT-P10 3.3, there was a higher incidence of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) leading to discontinuation, and a higher incidence of Grade 3 or higher TEAEs in the CT-P10 arm compared to the Rituxan arm. These observed differences created uncertainty as to whether there are no clinically meaningful differences between CT-P10 and Rituxan, but it was unclear given the design of the study whether these differences could be attributable to the background chemotherapy as well as differences between disease characteristics between treatment arms.

Study CT-P10 3.4

The Safety Analysis set consisted of 258 subjects who received at least one dose of either CT-P10 (n=130) or Rituxan (n=128). There were slightly more Grade 3 and higher adverse events, serious adverse events and drug discontinuations due to treatment-emergent adverse events in the CT-P10 group. There were two deaths in the CT-P10 group and no deaths in the Rituxan group. The absolute differences observed between arms in Study CT-P10 3.4 were generally less than those observed in Study CT-P10 3.3. The most common adverse events in patients with low tumor burden follicular lymphoma were infusion-related reactions, fatigue, diarrhea and upper respiratory infections.

Due to the differences between the two studies in regards to patient population and treatment duration, an integrated analysis of the safety results was not performed. Overall, there were slight numerical differences identified between the two treatment groups in both clinical studies. However, these are not expected to be clinically meaningful. The majority of the adverse events reported in both of the studies were expected given the known biologic effects of Rituxan.

The safety reviewer noted the following: "In study CT-P10 3.3, there were more subjects who experienced Grade 3 and higher adverse events and SAEs in the CT-P10 treatment group. However, the trial design was such at that the numbers were small and did not allow for a

rigorous assessment of safety comparisons between the two treatment groups. In addition, the differences observed were likely confounded by the use of CVP backbone chemotherapy, as well as differences in the baseline occurrence of bone marrow involvement of disease. Study CT-P10 3.4 included a larger patient population and the results were not confounded by the use of concomitant chemotherapy. The differences in safety findings in study CT-P10 3.4 were not as pronounced. Taken together, the data from the two studies did not suggest meaningful differences between CT-P10 and Rituxan."

The clinical and statistical teams recommend approval for the resubmission application of CT-P10.

9. Advisory Committee Meeting

An Oncologic Drugs Advisory Committee meeting was held on October 10, 2018. The meeting discussion focused on whether (1) the evidence supports a demonstration that CT-P10 is highly similar to US-licensed Rituxan, notwithstanding minor differences in clinically inactive components, (2) whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan, and (3) whether there is adequate justification to support licensure for the proposed indications sought by the Applicant. The committee members unanimously agreed by voting sixteen (Yes) to zero (No) that the totality of the evidence presented (analytical, pharmacological, immunogenicity, and clinical) supported the licensure of CT-P10 as a biosimilar for the three proposed NHL indications.

9. Pediatrics

The Applicant submitted their agreed upon Initial Pediatric Study Plan with the initial BLA. For the indications being sought by the Applicant, the Agency is waiving the pediatric study requirement because necessary studies are impossible or highly impracticable because the conditions rarely occur in children. (b) (4)

10. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Financial disclosures:** In accordance with 21 CFR 54, the Applicant submitted the required financial disclosure requirement and certification for investigators on the following studies: CT-P10 1.1, CT-P10 1.3, CT-P10 3.2, CT-P10 3.3, CT-P10 3.4. No investigators or sub-investigators declared financial interests.
- **Other GCP issues:** None.
- **OSI audits:** During the previous review cycle, for Study CT-P10 3.2, three clinical sites were selected for inspection. The inspections showed the clinical sites to be in compliance with Good Clinical Practices. For Study CT-P10 3.3, two clinical sites were selected for inspection. The final classification for the inspection for Dr. Sancho Cia's site in

Barcelona, Spain was Voluntary Action Indicated. Non-serious adverse events were not reported in two subjects, among other observations. Although regulatory violations were noted, it was deemed that they were unlikely to have a significant impact on the overall efficacy and safety of the study. The OSI investigators concluded that the data submitted from these clinical sites were reliable in support of the requested indication under this BLA. No additional clinical inspections were conducted as part of the resubmission.

There were no other outstanding regulatory issues.

11. Labeling

Labeling negotiations were ongoing at the time of this review.

12. Recommendations

- Recommended Regulatory Action: Approval

  All review disciplines recommend approval. Based on the above, we recommend approval for BLA 761088 for CT-P10 as a biosimilar to U.S.-licensed Rituxan for the following indications for which US-licensed Rituxan is currently licensed and for which Celltrion is seeking licensure:

  Adult patients with 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 a rituximab product 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.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Not Applicable.

- Recommendation for other Postmarketing Requirements and Commitments
  Not Applicable.

Acting Clinical Team Leader
Vishal Bhatnagar, MD

Cross Discipline Team Leader
Nicole Gormley, MD

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VISHAL BHATNAGAR
11/28/2018

NICOLE J GORMLEY
11/28/2018