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RESEARCH**

APPLICATION NUMBER:

761088Orig1s000

CLINICAL REVIEW(S)

SUMMARY REVIEW FOR REGULATORY ACTION

Application Number	BLA 761088
Application Type	351(k) BLA
Applicant	Celltrion,
Date of Receipt	05/29/2018
BSUFA Goal Date	11/29/2018
Division/Office	DHP/OHOP
Division Director	Ann T. Farrell, MD
Proposed Proprietary Name	Truxima*
Proposed Proper Name	Rituximab-abbs*
Dosage form(s) / Strength(s)	Injection: 100 mg/10 mL (10 mg/ml) and 500 mg/50 mL (10 mg/ml) solution in single-use vials
Approved Indications	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 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 on Regulatory Action	Approval

* For purposes of this review, the proposed product is referred to by either the proposed proprietary name, the proposed nonproprietary name, or the Applicant’s descriptor CT-P10. The proposed proprietary name, Truxima, and the proposed nonproprietary name, rituximab-abbs, are only conditionally accepted until the application is approved.

SUMMARY REVIEW FOR REGULATORY ACTION

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 Application received a complete response letter on February 28, 2018 because of identified facility, product quality and clinical deficiencies.

On May 29, 2018, Celltrion, Inc., responded to the complete response letter and resubmitted BLA 761088 seeking approval of CT-P10 as a biosimilar to US- licensed Rituxan (US-Rituxan).

The proposed indications are for 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 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.

In the May 2018 resubmission, Celltrion did not seek licensure for any other indications listed in the currently approved US-Rituxan label.

Reviews

The Product Quality Summary review concluded that CT-P10 is highly similar to US-Rituxan notwithstanding minor differences in clinically inactive components. Although minor differences in size variant profile, charge variant profile, deamidation, and glycosylation profile were observed, additional data and scientific justifications support that these differences do not preclude a finding that CT-P10 is highly similar to US-Rituxan. All previously identified product quality deficiencies in the complete response letter were resolved.

The Nonclinical review noted that the results of the comparative repeat-dose toxicity study in cynomolgus monkeys and tissue cross-reactivity study supported the demonstration of biosimilarity and concluded that the application was approvable.

The Clinical Pharmacology review recommended approval of CT-P10 based on a demonstration of pharmacokinetic (PK) similarity and no increase in immunogenicity risk between CT-P10 and US-Rituxan as demonstrated in Study CT -P10 3.2. Also included in the May 2018 resubmission was new pharmacokinetic information from the comparative clinical study CT-P10 3.4 conducted in patients with low tumor burden follicular lymphoma. 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.

All submitted clinical study data were reviewed. The Clinical review team agreed that the submitted data package supports a demonstration of no clinically meaningful differences between CT-P10 and US-Rituxan.

This application was discussed at an Oncologic Drugs Advisory Committee meeting on October 10, 2018. The meeting discussion focused on three issues: 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 unanimously agreed that the totality of analytical, pharmacologic, immunogenicity, and clinical evidence supports the demonstration that CT-P10 is highly similar to US-licensed Rituxan and that there are no clinically meaningful differences between them in the three proposed indications. The vote result was 16 to 0 in favor that the totality of evidence supports licensure of CT-P10 as a biosimilar product to US-Licensed Rituxan for the indications being sought.

Inspections

The facilities inspected were considered acceptable. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(c).

The clinical study sites inspection and the BIMO inspection did not uncover any findings which would impact the credibility of the clinical results.

Regulatory recommendation: Approval

I concur with the recommendation of the review teams that CT-P10 be approved as a biosimilar to US-Rituxan for the treatment of adult patients with non-Hodgkin's lymphoma (NHL) for the following indications;

- 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.

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/

ANN T FARRELL
11/28/2018

CLINICAL REVIEW

Application Type	Original 351(k)
Application Number(s)	BLA 761088
Priority or Standard	Class 2 resubmission
Submit Date(s)	May 29, 2018
Received Date(s)	May 29, 2018
BsUFA Goal Date	November 29, 2018
Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name(s)	Rachel Ershler, MD (Clinical Reviewer) Xin Gao, PhD (Statistical Reviewer)
Review Completion Date	October 25, 2018
Established Name	CT-P10
(Proposed) Trade Name	Truxima
Therapeutic Class	Proposed biosimilar to US-Rituximab
Applicant	Celltrion, Inc.
Formulation(s)	Injection for intravenous (IV) use
Dosing Regimen	375 mg/m ² IV infusion
Indication(s)	Non-Hodgkin's Lymphoma (NHL): 1. Relapsed or refractory, low grade or follicular CD20+ B-cell NHL as a single agent. 2. Previously untreated follicular, CD20+ 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. 3. Non-progressing (including stable disease), low grade, CD20+, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine and prednisone (CVP) chemotherapy.
Intended Population(s)	Non-Hodgkin's Lymphoma (NHL)

Template Version: March 6, 2009

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Table 1. List of Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BE	Bioequivalence
BID	Twice per day
BLA	Biologics License Application
BMI	Body mass index
CBC	Complete Blood Count
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, prednisone
DLBCL	Diffuse large B-cell lymphoma
DP	Drug product
DSN	Duration of severe neutropenia
ECG	Electrocardiogram
eCRF	Electronic case report form
eCTD	Electronic Common Technical Document
EOT	End of Treatment
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GPA	Granulomatosis with Polyangiitis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
Ig	Immunoglobulin
iPSP	Initial pediatric study plan
ISR	Injection site reactions
ISS	Integrated Safety Summary
IV	Intravenous

IWG	International Working Group
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
ML	Milliliters
MPA	Microscopic Polyangiitis
NAB	Neutralizing antibody
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
OSI	Office of Scientific Investigations
PD	Pharmacodynamic
PEG	Polyethylene glycol
PFS	Progression free survival
PHS	Public Health Service
PK	Pharmacokinetic
PLT	Platelet Count
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PV	Pemphigus Vulgaris
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable disease
TEAE	Treatment emergent AE
ULN	Upper limit of normal
WBC	White Blood Cell Count

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Biologics License Application (BLA) 761088 for CT-P10 (Truxima) was submitted by Celltrion, Inc. under section 351(k) of the Public Health Service Act. CT-P10 is a proposed biosimilar to US-licensed Rituxan[®]. Celltrion, Inc. is seeking licensure of CT-P10 for three of the Non-Hodgkin's Lymphoma (NHL) indications held by US-Rituxan[®]. The proposed indications are as follows:

1. Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
2. 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.
3. 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 (see Clinical Review by Anand Shah, October 13, 2017). A Complete Response was issued for clinical, product quality, and facility deficiencies. On May 28, 2018, the Applicant provided a resubmission to address the deficiencies identified in the CR letter.

To address the clinical deficiencies identified in the CR letter, and to support a demonstration of no clinically meaningful differences between CT-P10 and US-Rituxan[®] for the proposed indications being sought, the Applicant submitted additional long-term efficacy and safety data from Study CT-P10 3.3, as well as new clinical data from Study CT-P10 3.4 in low tumor burden follicular lymphoma (LTBFL).

Additional data was also submitted to support biosimilarity (see Product Quality and Clinical Pharmacology reviews for additional information).

This Clinical Reviewer recommends regular approval for CT-P10 (Truxima) for the indications being sought.

1.2 Risk Benefit Assessment

The clinical studies used to support this BLA for CT-P10 as a proposed biosimilar to US-licensed Rituxan® include:

- 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.

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 non-inferiority. However, the study was not designed to demonstrate equivalence. Inference about equivalence would be post-hoc and likely underpowered in this study.

Study CT-P10 3.4 used an equivalence design for the primary endpoint of ORR with equivalence margins of $\pm 17\%$. 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®.

A detailed analysis of safety outcomes was conducted using data from studies CT-P10 3.3 and CT-P10 3.4. Overall, there were slight numerical differences identified between the two treatment groups in both clinical studies. However, these were unlikely to be clinically meaningful. The majority of the adverse events reported in both of the studies were expected given the known biologic effects of rituximab.

Clinical efficacy and safety data support a demonstration that there are no clinically meaningful differences between CT-P10 and US-Rituxan®.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

Non-Hodgkin's Lymphoma (NHL) is the most common hematological malignancy in adults, with B-cell lymphomas comprising more than 80% of all NHLs. In 2018, it is estimated there will be more than 74,000 new cases of NHL including approximately 20,000 deaths (1). Since its U.S. approval in 1997, rituximab is widely considered to be a substantial advancement in the management of these malignancies. Multiple clinical studies have demonstrated the favorable impact of rituximab on treatment, survival, and long-term outcomes of patients with NHL and leukemia. There are currently no approved biosimilars to US- Rituxan®.

2.1 Product Information

Trade Name: TRUXIMA

Established Name: CT-P10

Dosage Forms: Injection: 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial

Therapeutic Class: Proposed biosimilar to US-Rituxan®

Chemical Class: B-lymphocyte antigen CD20 inhibitor

Mechanism of Action: CT-P10 is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab products mediate B-cell lysis.

Proposed Indication: Non-Hodgkin's Lymphoma (NHL)

Dosage/Administration: 375 mg/m²

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2. Summary of Treatments Relevant to Proposed Indication

Drug	Approval Date
Rituxan® (rituximab)	November 26, 1997
(b) (4)	

Source: FDA Clinical Reviewer

2.3 Availability of Proposed Active Ingredient in the United States

CTP-10 (Truxima) is not marketed in the United States.

Reference Product:

The reference product, US-Rituxan® was approved in 1997 and is currently marketed in the US 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.

2.4 Important Safety Issues With Consideration to Related Drugs

The Prescribing Information for US-Rituxan® list the following adverse reactions and Warnings and Precautions:

Most Common Adverse Reactions:

- NHL (≥25%): infusion reactions, fever, lymphopenia, chills, infection, asthenia
- CLL (≥25%): infusion reactions, neutropenia
- RA (≥10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, bronchitis
- GPA and MPA (≥15%): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema
- PV (≥15%): infusion reactions, depression

Boxed Warnings:

- Fatal infusion reactions within 24 hours of Rituxan® infusion
- Severe mucocutaneous reactions
- Hepatitis B virus (HBV) reactivation
- Progressive multifocal leukoencephalopathy (PML)

Additional Warnings and Precautions:

- Tumor lysis syndrome
- Infections
- Cardiac adverse reactions
- Renal toxicity
- Bowel obstruction and perforation
- Immunizations
- Embryo-Fetal toxicity

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The relevant regulatory history pertaining to the development of CT-P10 is detailed in the Table 3 below.

Table 3. CT-P10 Regulatory History

Date	Milestone
July 13, 2015	BPD Type 2 Meeting (IND 120885) • Discussion of the proposed development program • Obtain FDA feedback on Study CT-P10 3.3 and proposed design of CT-P10 3.2 extension
February 12, 2016	BPD Type 2 Meeting (IND 120885) • Discussion of the proposed development program for supporting registration of CT-P10 as a biosimilar to US-Rituxan®
January 17, 2017	BPD Type 3 Meeting (IND 120885) • Obtain FDA feedback regarding the similarity between CT-P10 and the reference product based on a comprehensive analytical data package • Reach an agreement on the CMC and analytical requirements in preparation for BLA submission
January 17, 2017	BPD Type 2 Meeting (IND 120885) • Obtain FDA concurrence and feedback on the proposed clinical development program with the data generated to date for the licensure of 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) • Obtain FDA agreement on the format and content of an application for CT-P10 to be submitted under section 351(k) of the PHS Act.
April 28, 2017	BLA 761088 Received

February 28, 2018	Complete Response Issued Clinical, product quality and facility deficiencies identified
April 16, 2018	BPD Type 1 Meeting (IND 120885) - Discuss issues and recommendations identified in the CR letter - Obtain agreement with the FDA on the proposed plan for resubmission
May 28, 2018	BLA 761088 Resubmitted to FDA

Source: FDA Clinical Reviewer

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 761088 was resubmitted on May 28, 2018 as an electronic submission in eCTD format. No clinical issues were identified during the filing review.

Clinical Reviewer Comment: *The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the applicant throughout the review process were addressed in a timely fashion.*

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies in the CT-P10 biosimilar clinical development program were conducted in compliance with Good Clinical Practice (GCP).

The Applicant disclosed that one clinical investigation site in study CT-P10 3.3 (Site #2804) was identified as GCP non-compliant due to scientific misconduct. This site was subsequently closed, and the patients enrolled at this site were excluded from all analysis populations except for the sensitivity analysis for the primary PK endpoint. There were no GCP noncompliant sites reported for study CT-P10 3.4, and the study was executed in accordance with GCP and International Council for Harmonization (ICH) standards.

3.3 Financial Disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the Applicant requested statements of financial interests from a total of 103 Principal Investigators and 477 sub-investigators for study CT-P10 3.4.

As of April 27, 2018, a total of 580 financial disclosures for the investigators who participated in this trial were received. There were no principal or sub-investigators who did not return the financial disclosure information. No investigators had financial information to disclose.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Chemistry Manufacturing and Controls (CMC) review.

4.2 Clinical Microbiology

See individual review of clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

See Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4. Tabular Listing of Clinical Studies

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/m ² 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/m ² IV	258 CT-P10: 130 US-Rituxan®: 128	153 sites in Europe, Asia, Latin America, North America	Ongoing Final CSR 2Q/2020

Source: FDA Clinical Reviewer

5.2 Review Strategy

The key materials used for the review of CT-P10 include:

- BLA datasets (raw and derived)
- Clinical study reports
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to information requests from the review team
- Major safety analyses were reproduced

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant submitted data from 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 (CT-P10 3.3) or low tumor burden follicular lymphoma (CT-P10 3.4).

5.3.1 Study CT-P10 3.3

Title: A Phase 1/3, Randomized, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison with Rituxan, Each Administered in Combination with Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients with Advanced Follicular Lymphoma

Clinical Site: 64 sites in Europe, Africa, Asia Pacific and Latin America

Study Period: July 28, 2014 – June 27, 2016

Population: Advanced Follicular Lymphoma

Study Design

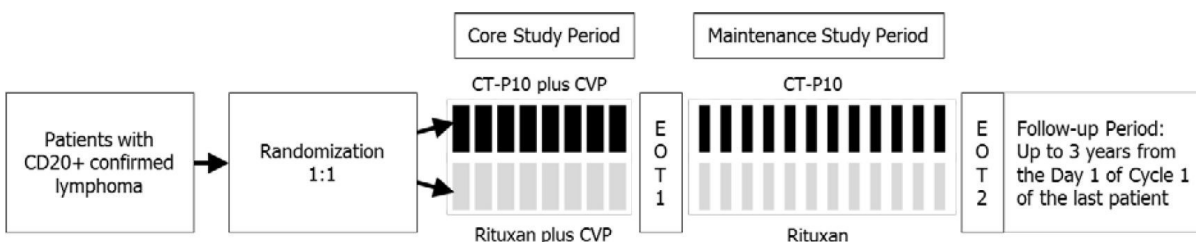
A Phase 1/3 prospective, randomized, parallel-group, active-controlled, double-blind, multicenter, international study with two primary endpoints designed to demonstrate similarity in pharmacokinetics (Part 1) and noninferiority in efficacy (Part 2) of CT-P10 to Rituxan when co-administered with CVP chemotherapy, and to assess pharmacodynamics and efficacy in patients with advanced (stage III-IV) CD20+ follicular lymphoma.

The study consisted of four periods:

- Screening Period (up to 4 weeks)
- Core Study Period (up to 8 cycles)
- Maintenance Study Period (up to 2 years)
- Follow-up Period (until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient)

The study design is depicted in Figure 1 below.

Figure 1. Study CT-P10 3.3 Schema



Source: Study CT-P10 3.3 CSR

Randomization and Stratification

Patients were randomly assigned to treatment groups using a computer-generated randomization schedule prepared before the study. The randomization was balanced by using permuted blocks and was stratified by country, gender, and Follicular Lymphoma International Prognostic Index (FLIPI) score (0 to 2 versus 3 to 5).

It was planned that approximately 134 patients were to be enrolled in this study in total.

- The initial 120 patients were to be enrolled in Part 1 and were to be randomly assigned in a 1:1 ratio to receive CT-P10 (approximately 60 patients) or Rituxan (approximately 60 patients) in combination with CVP. All subsequent patients were to be enrolled in Part 2.
- All patients from Part 1 of the study were to be included in Part 2 of the study and underwent all assessments performed in Part 2.
- In Part 2, approximately 134 patients (including the 120 patients from Part 1) were to be randomly assigned in a 1:1 ratio to CT-P10 (67 patients) or Rituxan (67 patients).

Core Study Period

Patients were screened within the 28 days prior to Day 1 of Cycle 1 of the Core Study Period.

During the Core Study Period, patients were treated with:

- Study Drug (CT-P10 or Rituxan)
 - On Day 1 of Cycle 1, patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study and were randomly assigned to receive either CT-P10 or Rituxan (375 mg/m² intravenous [IV]).
 - On the first day of each 21-day (±3 days) dosing cycle, patients received an IV infusion of study drug.
 - Premedication consisting of an antipyretic (e.g., paracetamol), an antihistamine (e.g., H1 antihistamine) and a glucocorticoid (prednisone or prednisolone [40 mg/m² orally]) was administered 30 minutes before each infusion of study drug.
- Cyclophosphamide
 - 750 mg/m² IV after infusion of study drug
- Vincristine
 - 1.4 mg/m² (up to a maximum of 2 mg) IV after infusion of study drug
- Prednisone or Prednisolone
 - 40 mg/m² orally on days 1 through 5 of each 21-day (±3 days) cycle.

Table 5. Study CT-P10 3.3: Route of Administration, Dose and Regimen of Treatment: Core Study Period

Study Treatment	Route of Administration	Dose	Frequency
Prednisone	Oral	40 mg/m ²	Days 1 through 5 of each 21-day cycle (for 8 cycles)
CT-P10 or Rituxan	IV infusion	375 mg/m ²	Day 1 of each 21-day cycle (for 8 cycles)
Cyclophosphamide	IV infusion	750 mg/m ²	
Vincristine	IV infusion	1.4 mg/m ²	

Source: Study CT-P10 3.3 CSR

Patients with stable or progressive disease during the Core Study Period were discontinued from study treatment and entered into the Follow-up Period. The first end-of-treatment (EOT1) visit occurred 3 weeks (±3 days) after the last dose of study drug in the Core Study Period. During the EOT1 visit, investigators determined whether patients qualified to continue in the Maintenance Study Period.

Maintenance Study Period

- Patients who experienced CR, CRu, or PR after Cycle 8 of the Core Study Period, as assessed at the first EOT visit, qualified for the Maintenance Study Period.
- If a patient withdrew before the completion of the Core Study Period, the patient was not entered into the Maintenance Study Period.
- The first dose in the Maintenance Study Period was administered after 2 months from the last dose in the Core Study Period (i.e., Day 1 of Cycle 8).
- Treatment included:
 - Study drug without CVP once every 2 months (±7 days) from the last dose of

- study drug for a maximum of 12 cycles (up to 2 years)
- Premedication: antipyretic (e.g., paracetamol), antihistamine and glucocorticoid 30 minutes prior to study drug
- The second EOT visit occurred 2 months (± 7 days) after the last dose of study drug in the Maintenance Study Period.

Follow-up Period

- Patients who did not qualify for the Maintenance Study Period and patients who completed the Maintenance Study Period entered the Follow-up Period 3 months from the last visit.
- The Follow-up Period was defined as until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient.
- Patients were monitored every 3 months for disease status, until treatment with new anticancer therapy or disease progression. Anticancer therapy and survival were to be monitored every 3 months until death or study termination.

Objectives

The overall objective was to demonstrate similar PK and noninferior efficacy of CT-P10 compared to Rituxan. This study was divided into 2 parts, each of which assessed different objectives and endpoints.

Primary Objectives:

- Part 1: Demonstrate that CT-P10 is similar to Rituxan in terms of PK as determined by AUC at steady state (AUC_{τ}) and maximum serum concentration at steady state ($C_{\max ss}$) at Core Cycle 4.
- Part 2: Demonstrate that CT-P10 is noninferior to Rituxan in terms of efficacy as determined by overall response rate (ORR)
 - 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

Secondary:

- Part 1: To evaluate other PK parameters of CT-P10 in comparison with Rituxan.
- Part 2:
 - To demonstrate ORR over 8 cycles in the Core Study Period according to the 2007 IWG criteria.
 - To evaluate additional efficacy parameters (progression-free survival, time to progression, time to treatment failure, response duration, disease-free survival, overall survival) according to the 1999 IWG criteria and the 2007 IWG criteria.
 - To evaluate PD, overall safety and biomarkers.

Key Inclusion Criteria

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

- Male or female 18 years or older
- Histologically confirmed FL according to the World Health Organization 2008 classification (Jaffe 2009); grades 1 to 3a based on local laboratory review.
- At least 1 measurable tumor mass that had not previously been irradiated, and the mass was:
 - nodal lesion >15 mm in the longest dimension; or
 - nodal lesion >10 mm to ≤15 mm in the longest dimension and >10 mm in the shortest dimension; or
 - extranodal lesion with both long and short dimensions ≥10 mm
- Confirmed CD20+ lymphoma, as assessed by local laboratory review
- Ann Arbor stage III or IV disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Oken *et al* 1982).
- For both male and female patients and their partners of childbearing potential, patient agreed to practice total abstinence or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study treatment (excluding women who were not of childbearing potential and men who were sterilized):
 - Barrier contraceptives (male condom, female condom or diaphragm with a spermicidal gel)
 - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
 - Intrauterine devices

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

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

- For both premenopausal women and women who were ≤ to 12 months after the onset of menopause, patient had a negative serum pregnancy test during the Screening Period.
- Adequate bone marrow, hepatic and renal function, as evidenced by:
 - Hemoglobin level ≥8 g/dL
 - Absolute neutrophil count (ANC) ≥1500/mm³
 - Platelet count ≥75000/mm³
 - Total bilirubin level ≤2.0 mg/dL
 - Aspartate aminotransferase and alanine aminotransferase levels ≤3x ULN (≤5x ULN with known hepatic involvement by lymphoma)
 - Serum creatinine level ≤1.5x ULN or a calculated creatinine clearance by the

Cockcroft-Gault equation of ≥ 50 mL/min

- Able to understand verbal and/or written instructions and comply with all study requirements.
- Informed, given ample time and opportunity to read and/or understand about participation in the study, and had signed and dated the written ICF.

Key Exclusion Criteria

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

- Received rituximab (or a rituximab proposed biosimilar product), cyclophosphamide, or vincristine.
- History of allergy or hypersensitivity to murine, chimeric, human or humanized proteins, cyclophosphamide, vincristine, or prednisone.
- Evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.
- Known central nervous system involvement.
- Received previous treatment for NHL:
 - Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy). However, patients who had received radiotherapy as part of the palliative therapy were eligible if the last fraction of radiotherapy was administered at least 4 weeks prior to Day 1 of Cycle 1 and patients had recovered from all radiotherapy-related toxicities prior to randomization.
 - All doses of glucocorticoid therapy for treatment of NHL.
 - Glucocorticoid therapy during the previous 4 weeks from Day 1 of Cycle 1, with prednisone >20 mg per day for any purpose.
- Current diagnosis of active tuberculosis (TB) (defined by chest x-ray, computed tomography [CT], or proper image) or other severe infections, such as sepsis, abscess, or opportunistic infections.
- Known infection with HIV, hepatitis B, or hepatitis C
- New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 6 months before Day 1 of Cycle 1.
- Any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before Day 1 of Cycle 1.
- Current or recent (within 30 days before Day 1 of Cycle 1) treatment with any other investigational medicinal product or device.
- Uncontrolled diabetes mellitus
- Pregnant or lactating. Patients who were planning to be pregnant or to breastfeed before, during, or within 12 months after the last infusion of study treatment were not permitted to enroll into the study.
- History of a live, live-attenuated, or non-live vaccine within 4 weeks before Day 1 of

Cycle 1 of study treatment.

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

Statistical Plan

Determination of Sample Size

Sample size was calculated based on the primary endpoint ORR (Part 2 of the Study CT-P10 3.3). A sample size of 134 patients (67 patients in each treatment arm) was planned to obtain 116 evaluable patients (58 patients in each treatment group), assuming 13% drop out rate. This sample size provided 80% power to demonstrate non-inferiority of CT-P10 vs. US-Rituxan[®] based on a non-inferiority margin of 7%. A post-hoc calculation indicated that this sample size was underpowered to demonstrate equivalence of CT-P10 versus US-Rituxan[®].

Non-inferiority Margin

The applicant proposed the non-inferiority margin of 7% based on historical studies (Marcus et al² and Federico et al³). In the Marcus 2005 historical study, MabThera had an 81% ORR (CR + CRu + PR) compared with CVP alone, which had a 57% ORR. In the Federico historical study, the ORR in the US-Rituxan[®] contained group was 88%. Based on the difference between these two studies, the 7% non-inferiority margin was selected.

A post hoc calculation was also done to estimate the non-inferiority margin based on the Marcus 2005 study², which is considered the only one relevant randomized study in the AFL setting. With the estimated risk difference of 0.24 (95% CI [0.145, 0.341]), a NI margin -7% preserved approximately 50% of the treatment effect of US-Rituxan[®], based on the lower bound of the 95% CI.

Analysis Populations

The primary analysis population was the intend-to-treat (ITT) population, defined as all randomized patients regardless of their actual treatment.

Safety Analyses

Safety analyses were performed by treatment group and included adverse events, serious adverse events (SAEs), hypersensitivity reactions, physical examination findings, vital sign measurements, clinical laboratory analyses, electrocardiogram (ECG) findings, ECOG performance status, infection, infusion-related reactions (IRRs), immunogenicity and immunoglobulin measurements

Key Protocol Revisions

A total of 11 minor country-specific and global protocol amendments are listed in the CSR. Most notable were global protocol amendments related to study eligibility criteria and statistical considerations in the amendment dated July 24, 2014.

Changes to the Statistical Analysis Plan (SAP)

The protocol stated that the per protocol population (PP) was defined as all randomly assigned patients who had at least one response evaluation after receiving at least one treatment cycle in the Core Study Period, and who did not have any major protocol violations, including a violation of the inclusion and exclusion criteria. To clarify the major protocol violation of the inclusion and exclusion criteria, the list of the inclusion and exclusion criteria, which has an impact on efficacy analysis, were presented in the SAP to define the PP population before the first database lock.

Statistical Reviewer Comments: *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.*

5.3.2 Study CT-P10 3.4

Title: A Phase 3, Randomized, Parallel-Group, Active-Controlled, Double-Blind Study to Compare Efficacy and Safety between CT-P10 and Rituxan in Patients with Low Tumor Burden Follicular Lymphoma

Clinical Site: 153 study centers in Europe, Asia Pacific, Latin America and North America.

Study Period: November 9, 2015 – Ongoing (database lock: February 23, 2018)

Population: Low tumor burden follicular lymphoma (LTBFL)

Study Design

This is a Phase 3, prospective, randomized, parallel-group, active-controlled, double-blind, multicenter, international study to compare the efficacy and safety of CT-P10 and Rituxan in patients with Grade 1 to Grade 3a, Ann Arbor stage II-IV, LTBFL based on Groupe d'Etudes des Lymphomes folliculaires (GELF) criteria.

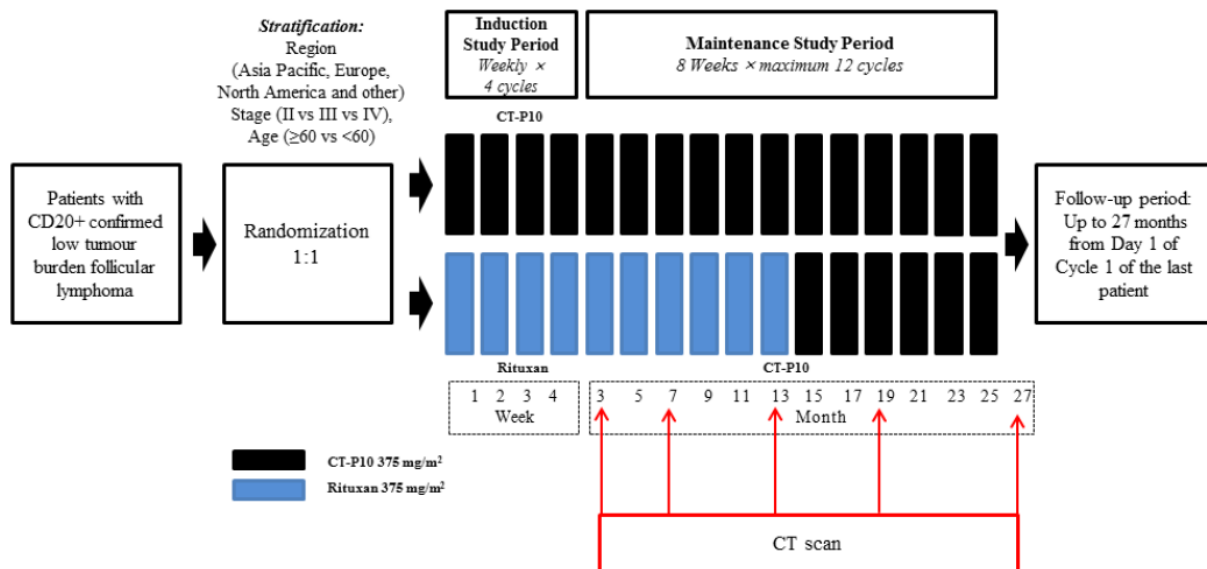
Patients were randomly assigned 1:1 to either CT-P10 or Rituxan and were stratified by region (Asia Pacific vs. Europe vs. North America and other), Ann Arbor stage (II vs. III vs. IV), and age (≥ 60 vs. < 60 years).

This study included 4 periods:

- Screening Period (up to 6 weeks)
- Induction Study Period (up to 4 weeks): Patients received study drug at a dose of 375 mg/m² IV once weekly for 4 weeks.
- Maintenance Study Period (up to a maximum of 12 cycles over 2 years): Patients who experienced a CR, CRu, PR or stable disease after Cycle 4 of the Induction Study Period (as assessed at the Maintenance 1 visit) were eligible to start maintenance therapy with the study drug at a dose of 375 mg/m² IV every 8 weeks. After the first year of the Maintenance Period (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 investigator.
- Follow-up Period (up to 27 months from Day 1 of Cycle 1 of the Induction Study Period for the last patient)

The study design is depicted in Figure 2 below.

Figure 2. Study CT-P10 3.4 Schema



Source: Study CT-P10 3.4 CSR

Duration of Treatment

Patients were treated with study drug weekly for up to 4 weeks in the Induction Study Period. Patients who experienced a CR, CRu, PR, or stable disease after the completion of the Induction Study Period (as assessed at the Maintenance 1 visit) were eligible to continue to receiving treatment with study drug once every 8 weeks for a maximum 12 cycles over 2 years in the Maintenance Study Period. 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 study duration up to the end of the study, including the Follow-Up Period, was up to 27 months from Day 1 of Cycle 1 of the Induction Study Period for the last patient.

Objectives

Primary Objective:

- To demonstrate that CT-P10 is similar to Rituxan in terms of efficacy as determined by the ORR at 7 months (prior to MC3) according to the Modified Response Criteria for Malignant Lymphoma.

Secondary Objectives:

- To evaluate ORR according to the Modified Response Criteria for Malignant Lymphoma.
- To evaluate PK, PD, overall safety, immunogenicity and biomarkers of CT-P10 in comparison with Rituxan.

Key Inclusion Criteria

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

- Male or female ≥ 18 years old
- Histologically confirmed CD20+ FL Grade 1 to 3a according to the World Health Organization 2008 classification; biopsy within 3 months of study drug treatment
- At least 1 measurable tumor mass in 2 dimensions, and the mass must be:
 - Nodal lesion >15 mm in the longest dimension
 - Nodal lesion >10 mm to ≤ 15 mm in the longest dimension and >10 mm in the shortest dimension, or
 - Extranodal lesion
- Ann Arbor stage II, III or IV disease
- Low tumor burden, defined based on GELF criteria:
 - No B symptoms
 - Normal LDH
 - Largest nodal or extra mass <7 cm
 - <3 nodal sites with a diameter ≥ 3 cm
 - No significant serous effusions detectable clinically or on CT
 - Spleen ≤ 16 cm CT
 - No clinical organ failure or organ compression
- ECOG performance status of 0 to 1

- For both male and female patients and their partners of childbearing potential, patient agrees to practice total abstinence or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):

- Barrier contraceptives
- Hormonal contraceptives
- Intrauterine devices

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

Menopausal female must have experienced their last period more than 12 months prior to study entry to be classified as not of childbearing potential.

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

- Adequate bone marrow, hepatic and renal function, as evidenced by:
 - Hemoglobin level ≥ 10 g/dL
 - Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Total bilirubin level ≤ 2.0 mg/dL
 - Aspartate aminotransferase and alanine aminotransferase levels ≤ 3 x ULN (≤ 5 x ULN with known hepatic involvement by lymphoma)
 - Serum creatinine level ≤ 1.5 x ULN or a calculated creatinine clearance by the Cockcroft-Gault equation of ≥ 50 mL/min
- Able to understand verbal and/or written instructions and comply with all study requirements.
- Patient is informed, given ample time and opportunity to read and/or understand about participation in the study, and has signed and dated the written informed consent.

Key Exclusion Criteria

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

- Received rituximab (or a rituximab proposed biosimilar product)
- History of allergy or hypersensitivity to contrast agents for radiograph, murine, chimeric, human or humanized proteins.
- Evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.
- Known central nervous system involvement.
- Received previous treatment for NHL:
 - Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy).

- All doses of glucocorticoid therapy for treatment of NHL.
- Glucocorticoid therapy during the previous 4 weeks before the first administration of the study drug with prednisone >20 mg per day for any purpose except NHL.
- Current diagnosis of active tuberculosis (TB) (defined by chest x-ray, computed tomography [CT], or proper image) or other severe infections, such as sepsis, abscess, or opportunistic infections.
- Known infection with HIV, hepatitis B, or hepatitis C
- New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 6 months before the first administration of study drug.
- Any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before the first administration of the study drug.
- Current or recent treatment (within 42 days before the first administration of the study drug or 5x the half-life, whichever is longer, prior to screening) with any other investigational medicinal product or device.
- Uncontrolled diabetes mellitus
- Pregnant or lactating. Patients who were planning to be pregnant or to breastfeed before, during, or within 12 months after the last infusion of study treatment were not permitted to enroll into the study.
- History of a live, live-attenuated, or non-live vaccine within 4 weeks before the first administration of the drug.
- Evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational product, or patient was a high risk for treatment complications.

Statistical Plan

Determination of Sample Size

A sample size of 174 patients (87 patients in each treatment group) was planned with 91% power to demonstrate equivalence of CT-P10 vs. US-Rituxan[®] using ORR up to 7 months. This calculation was based on an ORR of 88% in the US-Rituxan[®] treated group and an equivalence margin of $\pm 17\%$, using a 2-sided 90% CI approach.

During the trial, 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. A reassessment of sample size accounting for the actual dropout rate and the observed ORR was done in a blinded manner, and the sample size was increased to at least 238 patients (maximum 250) to achieve 80% power for the study.

Equivalence Margin

The equivalence margin of $\pm 17\%$ 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 Ardeshta et al (2014)⁴. The historical efficacy of rituximab based on the difference in ORRs 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 effect of rituximab for the equivalence trial was conservatively estimated as 75%. By applying a 77% preservation rate, the equivalence margin was proposed as $\pm 17\%$.

Analysis Populations

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.

Safety Analyses

Safety assessments included adverse events (AEs), serious AEs, concomitant medications, hypersensitivity reactions, physical examination findings, vital sign measurements, clinical laboratory analyses, chest x-ray findings, ECG findings, infections, infusion-related reactions, immunogenicity, immunoglobulin evaluation, and tuberculosis assessment.

Key Protocol Revisions

A total of 12 minor country-specific and global protocol amendments are listed in the CSR. Most notable were global protocol amendments related to study eligibility criteria and statistical considerations in the amendment dated August 6, 2015.

Changes to the Statistical Analysis Plan (SAP)

There were no changes to the planned analyses.

6 Review of Efficacy

Summary of Clinical Efficacy

Analyses of comparative clinical study data were based on study CT-P10 3.3 and study CT-P10 3.4. Both studies were randomized, double-blind, 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).

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 non-inferiority. However, the study was not designed to demonstrate equivalence. Inference about equivalence would be post-hoc and likely underpowered in this study.

Study CT-P10 3.4 used an equivalence design for the primary endpoint of ORR with equivalence margins of $\pm 17\%$. 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[®]. The results of tipping point analysis showed that the analysis result was robust with respect to the missing data.

6.1 Study CT-P10 3.3

6.1.1 Methods

Comparative Clinical Primary Endpoint

The primary endpoint of ORR in each treatment group and the difference in the ORR between the two treatment groups were calculated using an exact binomial method with 90% CI. To demonstrate NI, the 95% CI of the difference in ORR should lie completely above the NI margin of -7%.

Other Comparative Clinical Endpoints

Time-to-event secondary endpoints were analyzed descriptively based on the Kaplan-Meier method.

Analysis Populations

The primary analysis population was the Intent-to-treat (ITT) population, defined as all randomized patients regardless of the actual treatment group.

Sensitivity Analysis for Primary and Secondary Endpoint

No additional sensitivity analysis was performed for the primary endpoint, as the Agency did not agree with the study design.

Missing data Handling Strategies and Supportive Analyses

No additional missing data sensitivity analysis was performed for the primary endpoint.

6.1.2 Demographics

The demographics and baseline disease characteristics of subjects enrolled in study CT-P10 3.3 are summarized in the tables below. All patients were from Europe. In general, the demographic and baseline disease characteristics were balanced between the arms.

Table 6. Study CT-P10 3.3: Baseline Demographics and Disease Characteristics

Parameter Statistics	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Age (years)			
n	70	70	140
Mean (SD)	55.0 (13.76)	56.5 (14.12)	55.8 (13.91)
Median	57.0	58.5	57.5
Minimum, maximum	30, 85	26, 84	26, 85
Gender			
Male	30 (42.9)	33 (47.1)	63 (45.0)
Female	40 (57.1)	37 (52.9)	77 (55.0)
Height (cm)			
n	70	70	140
Mean (SD)	166.9 (9.19)	164.9 (9.83)	165.9 (9.53)
Median	166.0	165.0	165.5
Minimum, maximum	142, 188	145, 188	142, 188
Weight (kg)			
n	70	70	140
Mean (SD)	73.17 (15.669)	72.00 (15.317)	72.59 (15.449)
Median	71.00	71.25	71.00
Minimum, maximum	44.6, 130.0	43.7, 105.0	43.7, 130.0
Race			
White or Caucasian	51 (72.9)	52 (74.3)	103 (73.6)
Asian	11 (15.7)	13 (18.6)	24 (17.1)
Hispanic or Latino	6 (8.6)	3 (4.3)	9 (6.4)
Black or African American	2 (2.9)	0	2 (1.4)
Other	0	1 (1.4)	1 (0.7)
Not allowed by investigator country regulation	0	1 (1.4)	1 (0.7)
Region			
European Union	28 (40.0)	32 (45.7)	60 (42.9)
Non-European Union	42 (60.0)	38 (54.3)	80 (57.1)

Source: Study CT-P10 3.3 CSR

Table 7. Study CT-P10 3.3: ECOG Performance Status at Baseline

Parameter Statistics	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
ECOG performance status at screening			
0	44 (62.9)	47 (67.1)	91 (65.0)
1	25 (35.7)	22 (31.4)	47 (33.6)
2	1 (1.4)	1 (1.4)	2 (1.4)
3	0	0	0
4	0	0	0
5	0	0	0

Source: Study CT-P10 3.3 CSR

Table 8. Study CT-P10 3.3: Baseline Disease Characteristics

Parameter Result	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
	Number (%) of Patients		
Ann Arbor principal staging at screening			
Stage I	0	0	0
Stage II	0	0	0
Stage III	21 (30.0)	36 (51.4)	57 (40.7)
Stage IV	49 (70.0)	34 (48.6)	83 (59.3)
FLIPI score at screening			
0	0	0	0
1	8 (11.4)	6 (8.6)	14 (10.0)
2	25 (35.7)	21 (30.0)	46 (32.9)
3	23 (32.9)	30 (42.9)	53 (37.9)
4	10 (14.3)	12 (17.1)	22 (15.7)
5	4 (5.7)	1 (1.4)	5 (3.6)

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intent-to-treat.

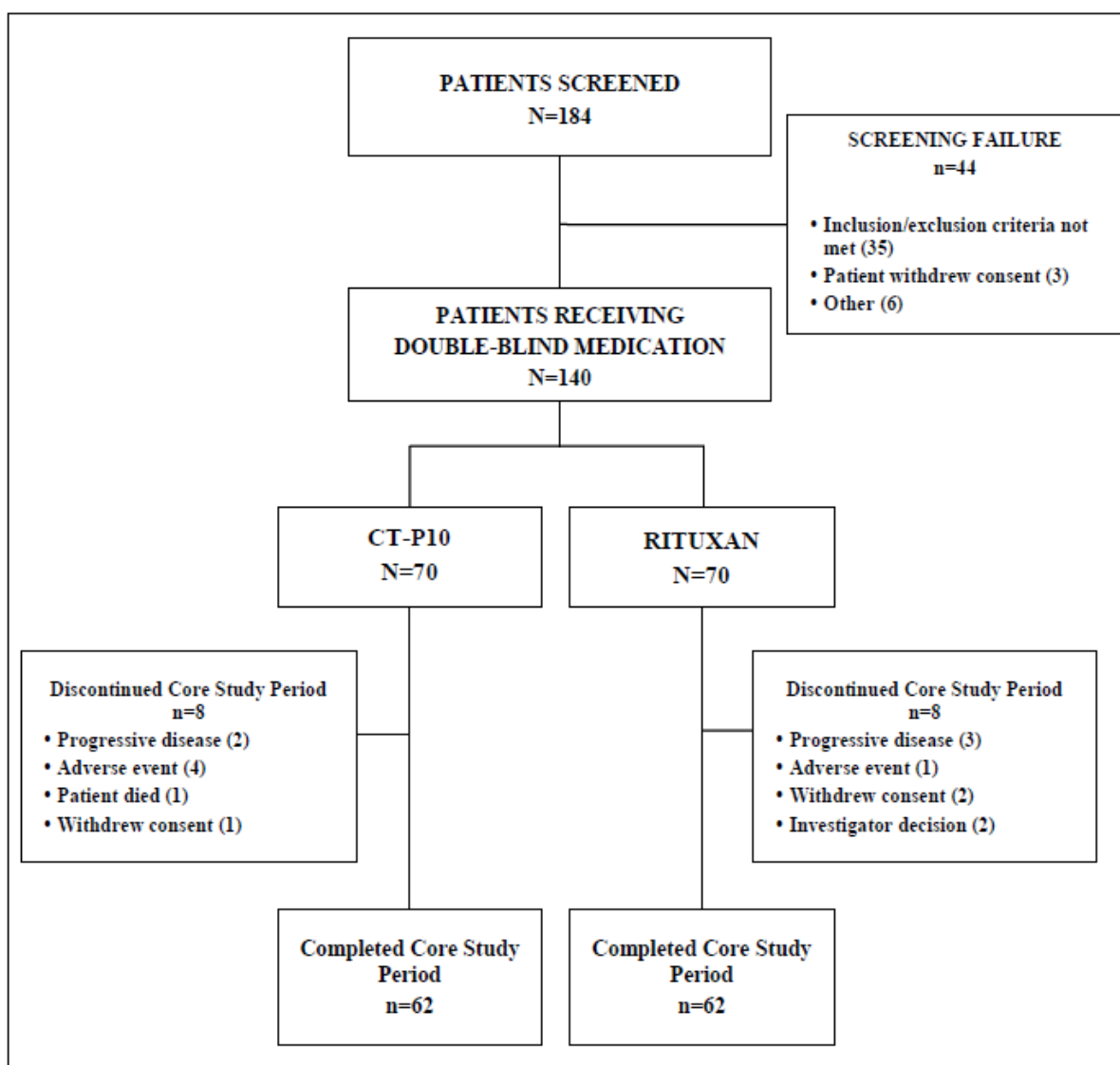
Source: Study CT-P10 3.3 CSR

Statistical Reviewer Comments: The Ann Arbor stage was imbalanced between the treatment groups (stage III 30% and stage IV 70% in the CT-P10 group versus stage III 51.4% and stage IV 48.6% in the Rituxan[®] arm). However, FLIPI score, which is a more comprehensive measurement of the disease status, appeared balanced between the two treatment groups. The FLIPI score was used as one of the stratification factors in the randomization. While the overall risk status appears, in general, to be balanced between the treatment groups, this does not assure the balance of the distribution in the components due to the small sample size of the trial.

6.1.3 Subject Disposition

A total of 140 patients were randomly assigned 1:1 to CT-P10 or US-Rituxan®. A summary of the subject disposition is provided in Figure 3 and Table 9. Overall, the disposition of subjects appeared balanced between the treatment groups. The number of subjects with early discontinuations due to adverse events was slightly higher in the CT-P10 group (n=4) compared to the US-Rituxan® group (n=1). However, the number of patients was too small to draw any conclusions.

Figure 3. Study CT-P10 3.3: Patient Disposition



Source: Study CT-P10 3.3 CSR, Figure 10-2

Table 9. Study CT-P10 3.3: Patient Disposition (ITT)

	CT-P10 (N=70)	Rituxan (N=70)	Total (N=140)
Number (%) of Patients			
Total number of patients in Part 2			
Screened ¹			184
Primary reason for screening failure ²			
Inclusion/exclusion criteria not met			35
Patient withdrew consent			3
Other			6
Randomized	70 (100.0)	70 (100.0)	140 (100.0)
Initiated core study treatment³			
Completed the Core Study Period	62 (88.6)	62 (88.6)	124 (88.6)
Early discontinued before completion of the Core Study Period	8 (11.4)	8 (11.4)	16 (11.4)
Primary reason for discontinuation			
Progressive disease ⁴	2 (2.9)	3 (4.3)	5 (3.6)
Adverse event ⁵	4 (5.7)	1 (1.4)	5 (3.6)
Patient died (tumour lysis syndrome) ⁶	1 (1.4)	0	1 (0.7)
Withdrew consent	1 (1.4)	2 (2.9)	3 (2.1)
Investigator decision ⁷	0	2 (2.9)	2 (1.4)
Number of deaths			
Reason for death			
Lymphoma ⁸	2 (2.9)	0	2 (1.4)
Adverse event (tumor lysis syndrome) ⁶	1 (1.4)	0	1 (0.7)

Abbreviation: ITT, intent-to-treat.

Note: Unless otherwise stated, percentages were calculated using the intent-to-treat population as the denominator.

- Includes screening failures and randomly assigned patients. If a patient was screened and randomly assigned, the treatment assigned was displayed in the “Randomized” row.
- This summary includes screening failures and nonrandomized patients only.
- Includes patients who were randomly assigned and initiated treatment.
- Last administered dose was Core Cycle 2 for Patient (b) (6) and Core Cycle 4 for Patient (b) (6) in the CT-P10 treatment group and Core Cycle 2 for Patient (b) (6), Core Cycle 4 for Patient (b) (6) and Core Cycle 7 for Patient (b) (6) in the Rituxan treatment group.

Source: Study CT-P10 3.3 CSR, Table 10-2

6.1.4 Analysis of Primary Endpoint(s)

The response status and the ORR difference are summarized in Table 10 and Table 11, respectively. Of note, study CT-P10 3.3 was not designed to show equivalence. The study was designed to show non-inferiority of CT-P10 vs. US-Rituxan®. Based on the

results, the study met the non-inferiority margin of -7%. Inference regarding equivalence would be post-hoc, and in this study is likely to be underpowered.

Table 10. Study CT-P10 3.3: Summary of ORR

	CT-P10 N=70 n(%)	US-Rituxan® N=70 n(%)
ORR (CR + CRu + PR)	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 (0)	1 (1.4)
Missing	1 (1.4)	2 (2.9)

Source: FDA Statistical Reviewer

Table 11. Study CT-P10 3.3: ORR Difference with 90% CI

	CT-P10 N=70	US-Rituxan® N=70
ORR	95.7% (88.1%, 98.5%)	90.0% (80.8%, 95.1%)
ORR difference	5.7% (90% CI, -1.7%, 14.7%)	

Source: FDA Statistical Reviewer

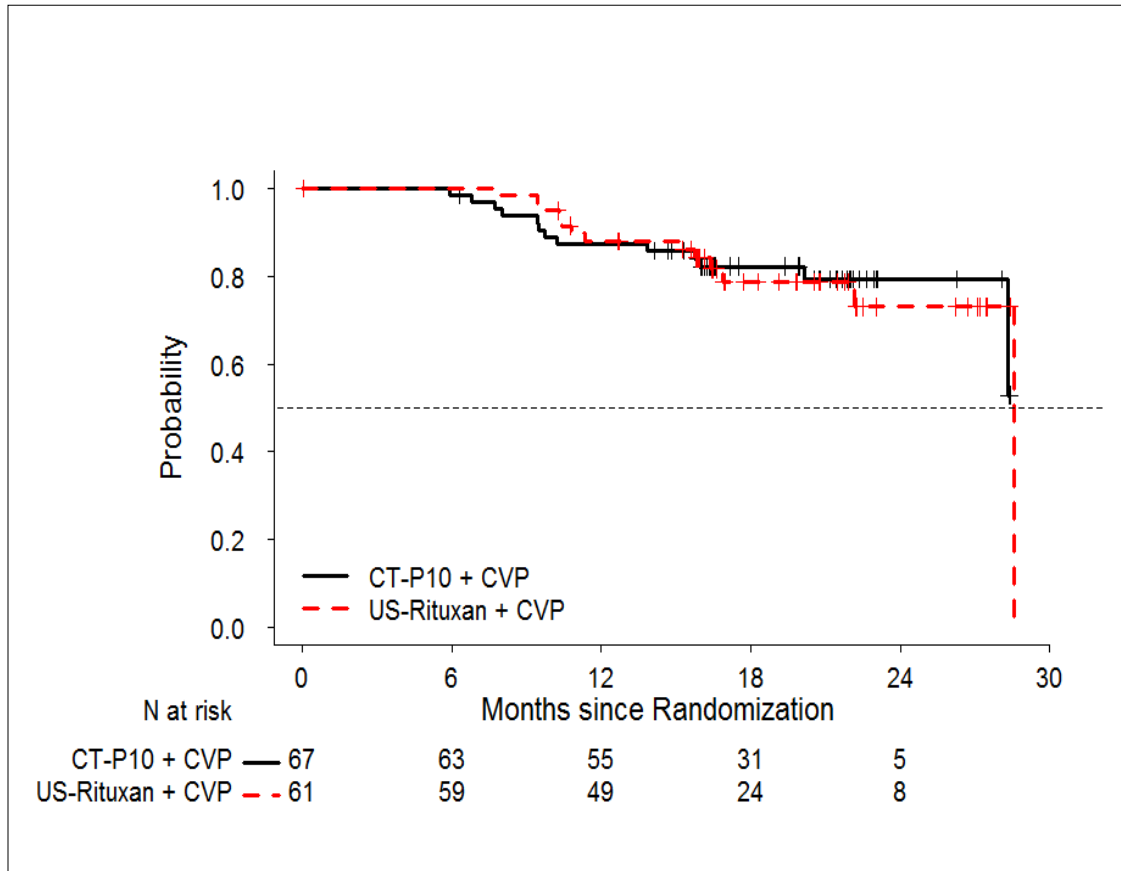
6.1.5 Analysis of Secondary Endpoints(s):

Duration of response, PFS and OS with cut-off date of July 2017 were analyzed with the Kaplan-Meier method. Of note, the response information for these endpoints was based on local review, rather than the central review response that was used for the primary endpoint, ORR. The central review for response was only available through the core study period. As a result, ORR was evaluated by the central review, while the duration of response could only be based on the investigator assessed responses since central review had not been performed for the follow-up period.

Duration of Response

The Kaplan Meier curves for the duration of response are plotted in Figure 4. Note these are not intended for comparative inference, as these represent the responders only. Among the responders, the duration of response appeared to be similar.

Figure 4. Study CT-P10 3.3: Kaplan-Meier Curves for Duration of Response

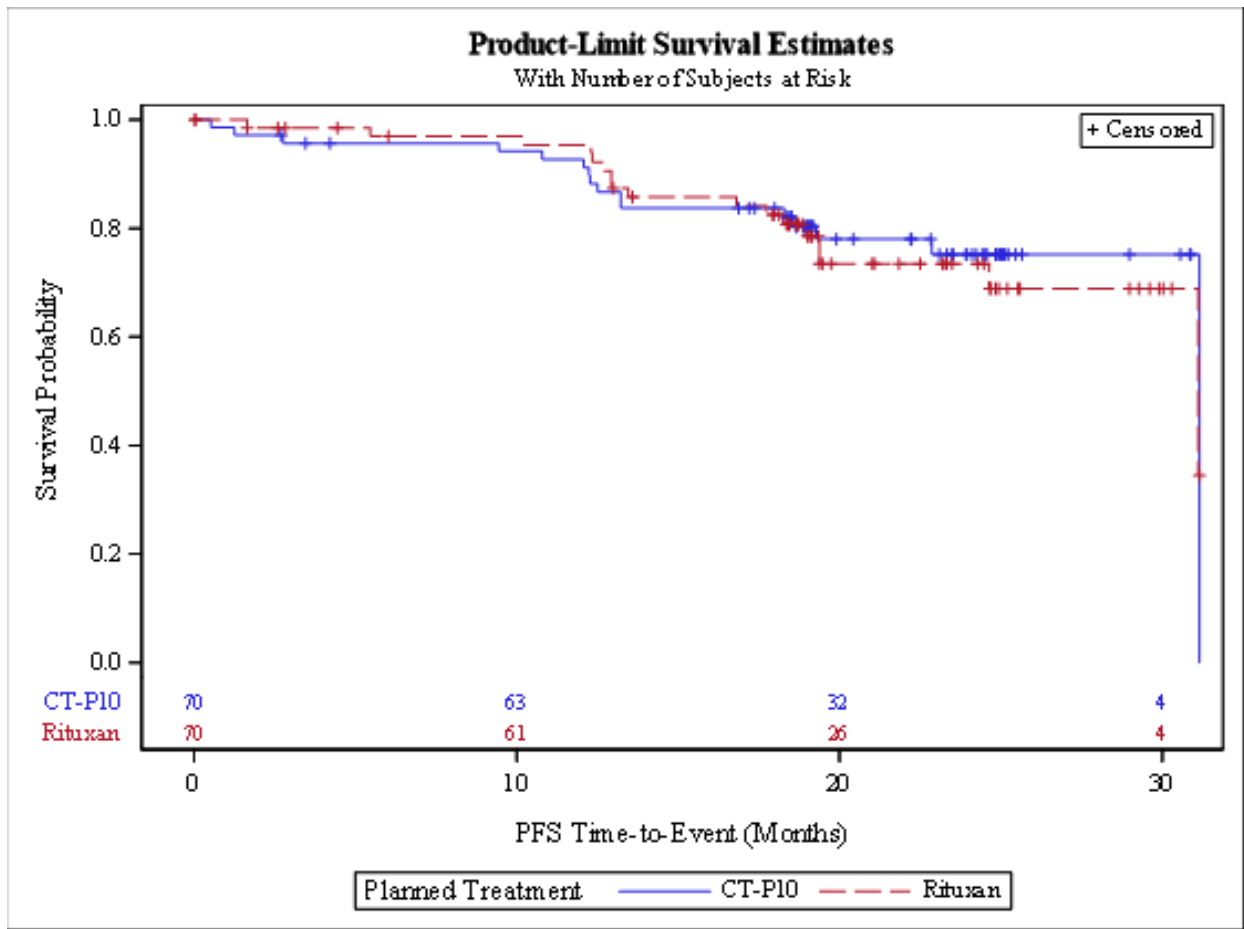


Source: FDA Statistical Reviewer

Progression Free Survival

The Kaplan Meier curves for PFS are plotted in Figure 5 below. The PFS appears to be similar between the two treatment groups.

Figure 5. Study CT-P10 3.3: Kaplan-Meier Curves for PFS

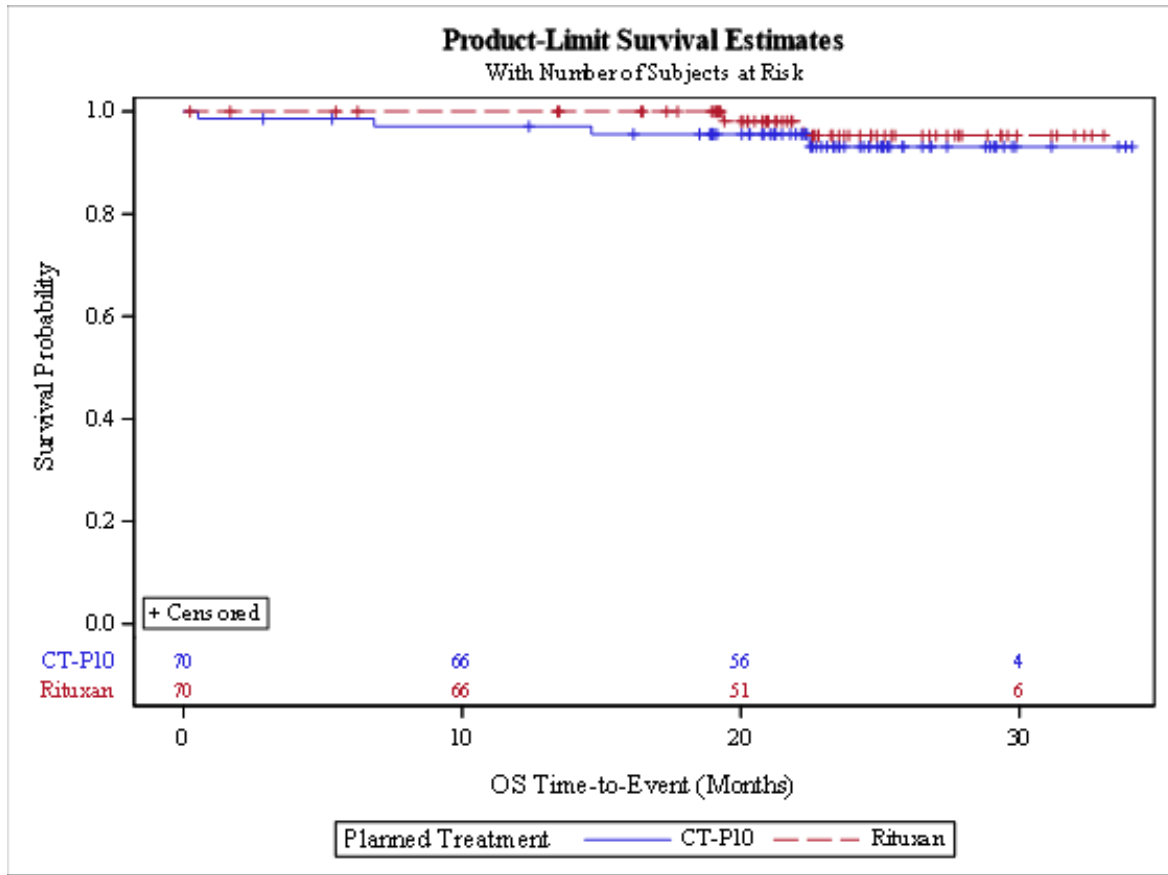


Source: FDA Statistical Reviewer

Overall Survival

The Kaplan Meier curves for the OS are plotted in Figure 6 below. The OS appears to be similar between the two treatment arms.

Figure 6. Study CT-P10 3.3: Kaplan-Meier Curves for OS



Source: FDA Statistical Reviewer

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The primary endpoint of ORR was analyzed in the subgroups of age, gender, race and geographic region. The results are summarized in Table 12. In some subgroups, the 90% CI interval was not entirely above the NI margin of -7%. However, as the subgroup analyses below were limited by the small sample size, the results need to be interpreted with caution.

Table 12. Study CT-P10 3.3: Subgroup Analysis of RR

Subgroup		CT-P10	Rituxan	Diff (90% CI)
Gender	Female	97.5% [87.1, 99.9]	97.3% [86.2, 99.9]	0.2% [-9.1, 11.3]
	Male	93.3% [78.7, 98.2]	81.8% [65.6, 91.4]	11.5% [-3%, 26.6%]
Race	White	96.1% [86.8, 98.9]	92.3% [81.8, 97]	3.8% [-4.7, 14.2]
	Non-white	94.7% [75.4, 99.7]	83.3% [60.8, 94.2]	11.4% [-7.4, 32]
Age	>60	96.6% [82.8, 99.8]	87.1% [71.1, 94.9]	9.5% [-5.8, 25.9]
	<=60	95.1% [83.9, 98.7]	92.3% [80, 97.3]	2.8% [-9.1, 14.8]
Geographic Region	European union	100% [87.9, 100]	90.6% [75.8, 96.8]	9.4% [-0.5, 24.7]
	Non-European union	92.9% [81, 97.4]	89.5% [75.9, 95.8]	3.4% [-8.6, 18.1]

Source: FDA Statistical Reviewer

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Comparative Clinical Study Results Issues/Analyses

Statistical Reviewer Comments: Several major issues were identified during the review of this Application. First, the Agency considers an equivalence design to be 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 patient population to detect differences between products could be influenced by the presence of concurrent background chemotherapy, and would require a large trial, which may not be feasible.

6.2 Study CT-P10 3.4

6.2.1 Methods

Comparative Clinical Primary Endpoint

The primary endpoint, best ORR by 7 months, and the difference of ORRs between the two treatment arms was analyzed by exact binomial methods with a 90% confidence interval. Equivalence was demonstrated if the 90% CI of the ORR difference lies entirely within the equivalence margins (-17%, 17%).

Other Comparative Clinical Endpoints

Time-to-event endpoints, such as duration of response, PFS and OS were analyzed with the Kaplan-Meier method.

Analysis Populations

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized patients, regardless of their actual treatment.

Sensitivity Analysis for Primary and Secondary Endpoint

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

Missing data Handling Strategies and Supportive Analyses

See above.

6.2.2 Demographics

The baseline demographics and disease characteristics for study CT-P10 3.4 are summarized in Table 13 and Table 14, respectively. The majority of the patients were from Europe and Asia Pacific. The mean age was 57.7 years in both treatment groups. The demographics and baseline disease characteristics appear to be balanced between the treatment groups, and there were no clinically meaningful differences between the two groups.

Table 13. Study CT-P10 3.4: Baseline Demographics and Disease Characteristics

	CT-P10 (N = 130)	US-Rituxan® (N = 128)	Total (N = 258)
Age			
Mean (SD)	57.7 (12.7)	57.7 (11.5)	57.7 (12.1)
Median (range)	58.0 (19 - 82)	59.0 (35 - 68)	58.5 (19 - 88)
Sex			
Male	66 (50.8%)	57 (44.5%)	123 (47.7%)
Female	64 (49.2%)	71 (55.5%)	135 (52.3%)
Race			
White	77 (59.2%)	75 (58.6%)	152 (58.9%)
Asian	47 (36.2%)	49 (38.3%)	96 (37.2%)
American Indian or Alaska Native	3 (2.3%)	3 (2.3%)	6 (2.3%)
Other	3 (2.3%)	1 (0.8%)	4 (1.6%)
Geographic Region			
North America	4 (3.1%)	4 (3.1%)	8 (3.1%)
Europe	67 (51.5%)	63 (49.2%)	130 (50.4%)
Asia Pacific	50 (38.5%)	51 (39.8%)	101 (39.1%)
Other	9 (6.9%)	10 (7.8%)	19 (7.4%)

Source: FDA Statistical Reviewer

Table 14. Study CT-P10 3.4: Other Baseline Disease Characteristics

	CT-P10 N = 130 n (%)	US-Rituxan N = 128 n (%)	Total N = 258 n (%)
ECOG Performance Score			
Score 0	109 (83.8)	108 (84.4)	217 (84.1)
Score 1	21 (16.2)	20 (15.6)	41 (15.9)
Ann Arbor Stage			
Stage I	1 (0.8)	0 (0)	1 (0.4)
Stage II	31 (23.8)	30 (23.4)	61 (23.6)
Stage III	47 (36.2)	53 (41.4)	100 (38.8)
Stage IV	51 (39.2)	45 (35.2)	96 (37.2)
FLIPI Score			
Score 0	18 (13.8)	17 (13.3)	35 (13.6)
Score 1	40 (30.8)	35 (27.3)	75 (29.1)
Score 2	46 (35.4)	49 (38.3)	95 (36.8)
Score 3	24 (18.5)	24 (18.8)	48 (18.6)
Score 4	2 (1.5)	3 (2.3)	5 (1.9)

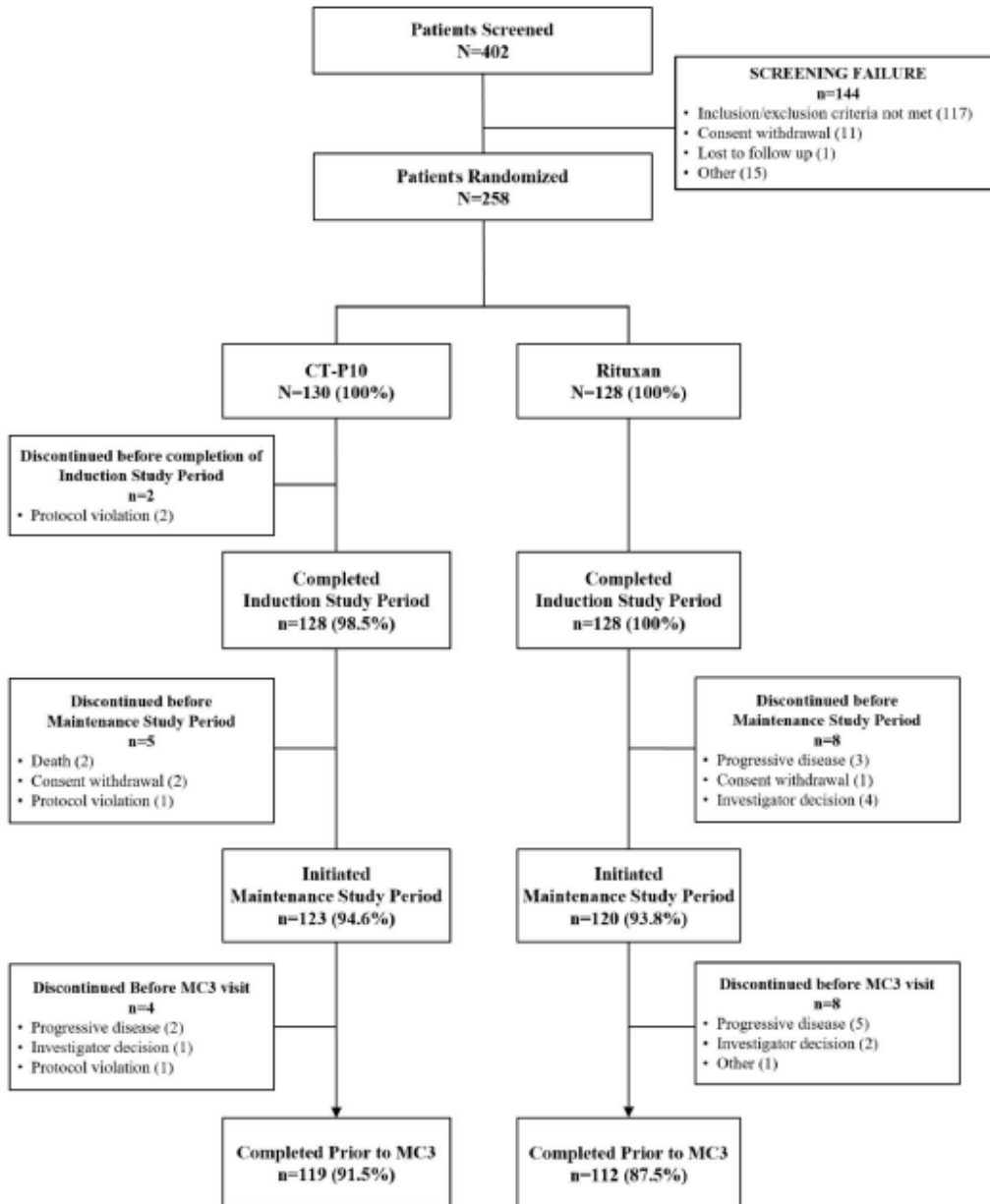
Source: FDA Statistical Reviewer

6.2.3 Subject Disposition

A total of 258 patients were randomly assigned 1:1 to CT-P10 or US-Rituxan®. The subject disposition is summarized in Figure 7 and Table 15. Overall, the subject

disposition appears balanced between treatment arms. Two subjects died in the CT-P10 group, and there were no deaths in the US-Rituxan® group. However, the number of patients was too small to draw any meaningful conclusions.

Figure 7. Study CT-P10 3.4: Patient Disposition



Abbreviation: MC3, Maintenance Cycle 3.

Source: Study CT-P10 3.4 CSR, Figure 10-1

Table 15. Study CT-P10 3.4: Patient Disposition (ITT)

	CT-P10 (N=130)	Rituxan (N=128)	Total (N=258)
Number (%) of patients			
Total number of patients			
Screened ¹			402
Primary reason for screening failure ²			
Inclusion/exclusion criteria not met			117
Consent withdrawal			11
Lost to follow up			1
Other			15
Randomized	130	128	258
Initiated induction period	130 (100.0)	128 (100.0)	258 (100.0)
Completed study treatment induction period	128 (98.5)	128 (100.0)	256 (99.2)
Discontinued study treatment during induction period	2 (1.5)	0	2 (0.8)
Primary reason for discontinuation			
Protocol violation ³	2 (1.5)	0	2 (0.8)
Completed induction but not entered into the maintenance period	5 (3.8)	8 (6.3)	13 (5.0)
Primary reason for discontinuation			
Progressive disease	0	3 (2.3)	3 (1.2)
Death ⁴	2 (1.5)	0	2 (0.8)
Consent withdrawal	2 (1.5)	1 (0.8)	3 (1.2)
Investigator decision ⁵	0	4 (3.1)	4 (1.6)
Protocol violation ³	1 (0.8)	0	1 (0.4)
Initiated maintenance period	123 (94.6)	120 (93.8)	243 (94.2)
Completed study treatment prior to MC3	119 (91.5)	112 (87.5)	231 (89.5)
Discontinued study treatment prior to MC3	4 (3.1)	8 (6.3)	12 (4.7)
Primary reason for discontinuation			
Progressive disease	2 (1.5)	5 (3.9)	7 (2.7)
Investigator decision ⁶	1 (0.8)	2 (1.6)	3 (1.2)
Protocol violation ³	1 (0.8)	0	1 (0.4)
Other	0	1 (0.8)	1 (0.4)
Reason for death			
Myocardial infarction ⁴	1 (0.8)	0	1 (0.4)
Respiratory failure ⁴	1 (0.8)		1 (0.4)

Abbreviations: EOT, end of treatment; IC, induction cycle; ITT, intent-to-treat; MC, maintenance cycle.

Note: Primary reason for discontinuation was summarized in consideration of specified discontinuation reason of each patient. The discontinuation reasons for 2 patients ((b) (6) CT-P10; (b) (6) Rituxan) were updated from other category in Post-text Table 14.1.1.

1. Included screening failures and randomly assigned patients.

2. Included screening failures only.
3. For patients with major protocol violation, it was advised to consider treatment discontinuation upon risk and benefit at the investigator's judgement. In total, 4 patients in the CT-P10 group discontinued study treatment due to protocol violation. Patient (b) (6) (had other malignancy of cervix cancer stage Ib), (b) (6) (received other rituximab proposed biosimilar product), (b) (6) (had other malignancy of squamous cell carcinoma of lung) and (b) (6) (violated GELF criteria) discontinued study treatment after IC2, IC3 and IC4 and MC2, respectively.
4. Two patients ((b) (6) CT-P10) died of myocardial infarction and respiratory failure secondary to bronchiolitis obliterans with organizing pneumonia, respectively, after IC4. Details are described in Section 12.3.1.1.
5. Three patients ((b) (6) Rituxan) discontinued study treatment as the investigator considered no maintenance therapy was required. For both central and local reviews, each patient had a response of PR, PR and stable disease at the EOT2 visit, respectively. Patient (b) (6) in the Rituxan group had a response of stable disease at the EOT2 visit by both central and local reviews, but discontinued study treatment because investigator suspected as progressive disease based on clinical experience.
6. Two patients discontinued study treatment per investigator's decision of progressive disease based on clinical experience: Patient (b) (6) in the CT-P10 group had a PR at MC1 by both central and local reviews. Patient (b) (6) in the Rituxan group had stable disease at the EOT3 visit by local review and progressive disease by central review. One patient (Patient (b) (6) Rituxan) discontinued study treatment to participate in another clinical trial by investigator's decision.

Source: Study CT-P10 3.4 CSR, Table 10-1

6.2.4 Analysis of Primary Endpoint(s)

Primary Analysis

ORR by central review was summarized for each treatment arm in the ITT population and PP population (see 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 lay within the equivalence margin of $\pm 17\%$. Therefore, the study demonstrated the equivalence between the CT-P10 and US-Rituxan®.

Table 16. 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%)	

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 (0)	4 (3.3)
Unable to Assess	0 (0)	1 (0.8)
ORR difference ¹	3.5% (-7.34%, 14.34%)	
ORR difference ²	3.5% (-4.49%, 11.43%)	
ORR difference ³	3.5% (-4.56%, 11.56%)	

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

Source: FDA Statistical Reviewer

Sensitivity Analysis

ORR by central review was also analyzed in the PP population (Table 16). In addition, the ORR by local review was analyzed in each treatment arm in the ITT population and the PP population (Table 17). In both the FDA analysis and the Applicant's analysis, the entire 90% CIs lay within the equivalence margin of $\pm 17\%$, indicating the primary analysis findings are robust for the review methods (central vs. local) and study population (ITT vs. PP).

Table 17. Study CT-P10 3.4: ORR Based on 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% (-13.69%, 6.77%)	
ORR difference ²	-3.5% (-12.32%, 5.31%)	
ORR difference ³	-3.5% (-12.36%, 5.63%)	
PP Population	N = 114	N = 120
Overall Response	90 (78.9)	96 (80.0)
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 (0)	3 (2.5)
Missing		
ORR difference ¹	-1.1% (-11.91%, 9.74%)	
ORR difference ²	-1.1% (-10.12%, 7.95%)	
ORR difference ³	-1.1% (-10.24%, 7.96%)	

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

Source: FDA Statistical Reviewer

Missing Data Sensitivity Analysis

Sensitivity analyses evaluating the possible impacts of missing data being imputed under various assumptions also fell within the $\pm 17\%$ margin, supporting the primary analysis conclusion that there are no clinically meaningful differences in ORRs between CT-P10 and US-Rituxan®.

Table 18. Study CT-P10 3.4: Tipping Point Analyses Based on Central Reviewed Response with Exact Binomial Method 1*

# of Responders 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)

*ITT population, confidence limits obtained by Farrington-Manning score statistic (Chan and Zhang 1999) in method 1

Source: FDA Statistical Reviewer

Table 19. Study CT-P10 3.4: Tipping Point Analyses Based on Central Reviewed Response with Exact Binomial Method 2*

# of Responders	US-Rituxan®		
	0	1	2
CT-P10			
0	1.83 (-8.31, 12.15)	1.05 (-9.08, 11.39)	0.26 (-9.85, 10.62)
1	2.60 (-7.54, 12.92)	1.81 (-8.31, 12.15)	1.03 (-9.08, 11.39)
2	3.37 (-6.77, 13.69)	2.58 (-7.54, 12.92)	1.80 (-8.31, 12.15)
3	4.13 (-6.00, 14.45)	3.35 (-6.77, 13.69)	2.57 (-7.54, 12.92)
4	4.90 (-5.22, 15.22)	4.12 (-6.00, 14.45)	3.34 (-6.77, 13.69)
5	5.67 (-4.45, 15.98)	4.89 (-5.22, 15.22)	4.11 (-6.00, 14.45)

*ITT population, confidence limits obtained by inverting two separate one-sided exact tests (Santner and Snell 1980) using the unstandardized risk difference

Source: FDA Statistical Reviewer

Table 20. Study CT-P10 3.4: Tipping Point Analysis Based on Local Reviewed Response with Exact Binomial Method 1*

# of Responders	US-Rituxan®	
	0	1
CT-P10		
0	-3.51 (-13.69, 6.77)	-4.29 (-14.45, 6.00)
1	-2.74 (-12.92, 7.54)	-3.52 (-13.69, 6.77)
2	-1.97 (-12.15, 8.31)	2.75 (-12.92, 7.54)
3	-1.20 (-11.39, 9.08)	-1.98 (-12.15, 8.31)
4	-0.43 (-10.62, 9.85)	-1.21 (-11.39, 9.08)
5	0.34 (-9.85, 10.62)	-0.44 (-10.62, 9.85)

* ITT population, confidence limits were obtained by inverting two separate one-sided exact tests (Santner and Snell 1980) using the unstandardized risk difference with method 1.

Source: FDA Statistical Reviewer

Table 21. Study CT-P10 3.4: Tipping Point Analyses Based on Local Reviewed Response with Exact Binomial Method 2*

# of Responders	US-Rituxan®	
	0	1
CT-P10		
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)

* ITT population, confidence limits were obtained by Farrington-Manning score statistic (Chan and Zhang 1999) with method 2.

Source: FDA Statistical Reviewer

6.2.5 Analysis of Secondary Endpoints(s):

Duration of Response (CR, CRu, or PR)

The median follow-up time was 6.3 months in the ITT population for both treatment groups. The number of patients with relapse or progression of disease after meeting the criteria for overall response were 1 (0.9%) and 2 (1.9%) in the CT-P10 and US-Rituxan® groups, respectively. The current data set is not mature for evaluation of duration of response.

Progression Free Survival

The number of patients with disease progression, relapse or death from any cause was 5 (3.8%) and 10 (7.8%) for the CT-P10 and US-Rituxan® groups, respectively. The median time of PFS is not estimable for either treatment arm. The current data set is not mature for evaluation of PFS.

Overall Survival

There were 2 deaths in the CT-P10 treatment group and no deaths in the US-Rituxan® treatment group. The median time of OS is not estimable in either treatment arm. The current data set is not mature for evaluation of OS.

6.2.6 Other Endpoints

Not applicable.

6.2.7 Subpopulations

The primary endpoint of ORR was analyzed in the subgroups of age, gender, race and geographic region. The results are summarized in Table 22. In some subgroups, the 90% CI interval was outside the equivalence margins. However, the results should be interpreted with caution, as the subgroup analyses were limited by the small sample size.

Table 22. Study CT-P10 3.4: Subgroup Analysis of ORR

	CT-P10 n/N (%)	US-Rituxan n/N (%)	Difference Method 1* (90% CI)	Difference Method 2* (90% CI)
Age				
< 65 years	68/84 (81.0)	72/90 (80.0)	0.95 (-11.65, 13.47)	0.95 (-9.22, 11.16)
≥ 65 years	40/46 (87.0)	32/38 (84.2)	2.75 (-15.12, 20.64)	2.75 (-10.45, 16.71)
< 60 years	52/66 (78.8)	52/66 (78.8)	0 (-14.96, 14.96)	0 (-11.98, 11.98)
≥ 60 years	56/64 (87.5)	52/62 (83.9)	3.63 (-10.72, 18.51)	3.63 (-7.42, 14.54)
Gender				
Male	54/66 (81.8)	41/57 (71.9%)	9.89 (-5.07, 24.47)	9.89 (-3.02, 22.80)
Female	54/64 (84.4)	63/71 (88.7%)	-4.36 (-18.44, 9.80)	-4.36 (-14.97, 5.72)
Race				
White or Caucasian	63/77 (81.8)	59/75 (78.7%)	3.15 (-10.07, 16.56)	3.15 (-7.95, 14.09)
Asian	40/47 (85.1)	42/49 (85.7%)	-0.61 (-17.72, 15.73)	-0.61 (-13.69, 12.25)
Other	5/6 (83.3%)	3/4 (75.0%)	8.33 (-46.35, 59.62)	-8.33 (-42.60, 59.62)
Region				
Europe	55/66 (83.3%)	51/63 (81.0%)	2.38 (-12.36, 17.09)	2.38 (-9.23, 14.07)
Asia Pacific	43/47 (91.5%)	42/50 (84.0%)	7.49 (-9.30, 24.28)	7.49 (-4.54, 19.21)
Other	10/17 (58.8%)	11/15 (73.3%)	-14.51 (-42.74, 14.33)	-14.51 (-42.31, 14.38)

* ITT population, central reviewed response. In method 1, confidence limits were obtained by inverting two separate one-sided exact tests (Santner and Snell 1980) using the unstandardized risk difference. In method 2, confidence limits were obtained by Farrington-Manning score statistic (Chan and Zhang 1999).

Source: FDA Statistical Reviewer

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.2.10 Additional Comparative Clinical Study Results Issues/Analyses

No major statistical issues were identified in the review of study CT-P10 3.4. The best ORR by 7 months was compared between the two treatment groups, and the 90% CI of the ORR difference lies entirely within the equivalence margins $\pm 17\%$, which demonstrated the equivalence of CT-P10 and US-Rituxan[®]. Sensitivity analyses by using PP population and local reviewed response data showed similar results, which demonstrates that the test of equivalence of CT-P10 vs. US-Rituxan[®] is robust to the analysis population and review methods. Additional missing data sensitivity analysis also support the results of equivalence between the treatment groups, indicating that the equivalence of CT-P10 vs. US-Rituxan based on ORR is robust to missing data.

One minor statistical issue is the small variation of the results based on exact binomial method for ORR analyses. Multiple algorithms may be potentially used in the calculation of the exact CI for the difference in ORRs, and the SAP did not pre-specify which one would be used for the analysis, which lead to some variations of the exact 90% CI of the difference in ORRs. It would be best to pre-specify which algorithm with the exact binomial method to be used in the analyses of ORR in the SAP.

Another issue is the unmatured data for the analyses of the secondary endpoints, including the duration of response, in Study CT-P10 3.4. However, the duration of response data in Study CT-P10 3.3 may provide supportive information for this endpoint.

7 Review of Safety

Safety Summary

A detailed analysis of safety outcomes was conducted using data from studies CT-P10 3.3 and CT-P10 3.4. 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. The safety populations for both studies consisted of all subjects who received at least one (full or partial) dose of study drug. Overall, there were slight numerical differences identified between the two treatment groups in both clinical studies. However, these were unlikely to be clinically meaningful. The majority of the adverse events reported in both of the studies were expected given the known biologic effects of rituximab. The most common adverse events in patients with advanced follicular lymphoma were neutropenia, infusion related reactions, constipation and upper respiratory infections. The most common adverse events in patients with low tumor burden follicular lymphoma were infusion related reactions, fatigue, diarrhea and upper respiratory infections.

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).

The majority of subjects in both treatment groups experienced at least one adverse event. 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.

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).

The majority of subjects in both treatment groups experienced at least one TEAE. 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.

Clinical Reviewer Comment: *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 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®.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety summary focuses on safety data from:

1. CT-P10 3.3: Phase 1/3, randomized, active-controlled, parallel-group, double-blind study to demonstrate equivalence of PK and non-inferiority of efficacy for CT-P10 in comparison with Rituxan, each administered with CVP chemotherapy in patients with advanced follicular lymphoma.
2. CT-P10 3.4: Phase 3, prospective, randomized, parallel-group, active-controlled, double-blind, multicenter, international study to compare the efficacy and safety of CT-P10 and Rituxan in patients with Grade 1 to Grade 3a, Ann Arbor stage II-IV, LTBFL based on GELF criteria.

The key data reviewed for clinical safety includes:

- Clinical study reports for CT-P10 3.3 and CT-P10 3.4
- Summaries of clinical safety for CT-P10 3.3 and CT-P10 3.4
- Clinical protocols and statistical analysis plans for CT-P10 3.3 and CT-P10 3.4
- Raw and derived datasets for CT-P10 3.3 and CT-P10 3.4
- Case report forms and narratives for CT-P10 3.3 and CT-P10 3.4

7.1.2 Categorization of Adverse Events

Adverse events were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.2 and graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All safety data were tabulated and listed by treatment group, as appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study CT-P10 3.3

In Study CT-P10 3.3, 62/70 (88.6%) patients in each treatment group received study drug (CT-P10 or Rituxan®) through Core Cycle 8.

During the Core Study Period (up to Core Cycle 8), the mean (SD) of relative dose intensity was similar between the two treatment groups; 97.7% (4.40%) and 98.3% (2.71%) in the CT-P10 and Rituxan® groups, respectively. Similarly, the median relative dose intensity during this time was 99.3% in the CT-P10 group and 99.0% in the Rituxan group.

The total number of patients whom received each dose during the Core Study Period (up to Core Cycle 8) is presented in the Table below.

Table 23. Study CT-P10 3.3 (Part 2): Overall Exposure up to Core Cycle 8 - Safety Population

	CT-P10 (N=70) n (%)	Rituxan® (N=70) n (%)	Total (N=140) n (%)
Core Cycle 1 at Week 0	70 (100.0)	70 (100.0)	140 (100.0)
Core Cycle 2 at Week 3	69 (98.6)	68 (97.1)	137 (97.9)
Core Cycle 3 at Week 6	68 (97.1)	66 (94.3)	134 (95.7)
Core Cycle 4 at Week 9	66 (94.3)	66 (94.3)	132 (94.3)
Core Cycle 5 at Week 12	64 (91.4)	65 (92.9)	129 (92.1)
Core Cycle 6 at Week 15	63 (90.0)	64 (91.4)	127 (90.7)
Core Cycle 7 at Week 18	62 (88.6)	63 (90.0)	125 (89.3)

Source: Summary of Clinical Safety, Table 2.7.4-4

Study CT-P10 3.4

In Study CT-P10 3.4, 258 subjects were randomized and 256 (99.2%) received the study drug through Cycle 4 of the Induction Study Period (128/130 [98.5%] in the CT-P10 group and 128/128 [100%] in the Rituxan® group). The majority of patients, 123/130 (94.6%) and 11/128 (92.2%) patients in the CT-P10 and Rituxan® groups, respectively, received study drug through 2 cycles of the Maintenance Study Period.

The total number of patients who received each dose through 2 cycles of the Maintenance Study Period is presented in the Table below.

Table 24. Study CT-P10 3.4: Overall Exposure - Safety Population

	CT-P10 (N=130) n (%)	Rituxan® (N=128) n (%)	Total (N=258) n (%)
Induction Study Period			
Induction Cycle 1 at Week 1	130 (100.0)	128 (100.0)	258 (100.0)
Induction Cycle 2 at Week 2	130 (100.0)	128 (100.0)	258 (100.0)
Induction Cycle 3 at Week 3	129 (99.2)	128 (100.0)	257 (99.6)
Induction Cycle 4 at Week 4	128 (98.5)	128 (100.0)	256 (99.2)
Maintenance Study Period			
Maintenance Cycle 1 at Week 12	123 (94.6)	120 (93.8)	243 (94.2)
Maintenance Cycle 2 at Week 20	123 (94.6)	118 (92.2)	241 (93.4)

Source: Summary of Clinical Safety, Table 2.7.4-5

The average daily dose and number of dose interruptions for both treatment groups is depicted in the Table below.

Table 25. Study CT-P10 3.4: Average Dose and Dose Interruptions - Safety Population

	CT-P10 (N=130) n (%)	Rituxan® (N=128) n (%)
Average daily dose (mg/m ² /week) prior to MC3* Mean (SD)	125.0 (56.74)	129.2 (63.4)
Dose Interruptions	39 (30.0)	36 (28.1)

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: The overall exposure was similar in the two treatment groups in Study CT-P10 3.4.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Blood samples (including samples for beta-2 microglobulin) and urine samples for clinical laboratory assessments were collected at the time points specified in the Study CT-P10 3.3 and CT-P10 3.4 protocols.

Clinical Reviewer Comment: The frequency of monitoring was adequate to assess the safety of CT-P10.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse events for similar drugs in drug class was reviewed in Section 2.4 Important Safety Issues with Consideration to Related Drugs.

7.3 Major Safety Results

An overview of the major safety findings for Study CT-P10 3.3 and Study CT-P10 3.4 are shown in Tables 26 and 27, respectively.

Table 26. Study CT-P10 3.3 - Summary of Safety Results

	CT-P10 N=70 n(%)	Rituxan® N=70 n(%)
Subjects With at Least one TEAE	63 (90.0)	60 (85.7)
Subjects With Grade ≥3 TEAE	36 (51.4)	28 (40.0)
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)
Fatal TEAEs	3 (4.3)	1 (1.4)

Source: FDA Clinical Reviewer

Table 27. Study CT-P10 3.4 Summary of Safety Results

	CT-P10 N=130 n(%)	Rituxan N=128 n(%)	Total N=258 n(%)
Subjects with ≥ 1 TEAE	94 (72.3)	90 (70.3)	184 (71.3)
Number of subjects with ≥ 1 TEAE by severity			
Grade 1	17 (13.1)	15 (11.7)	32 (12.4)
Grade 2	63 (48.5)	63 (49.2)	126 (48.8)
Grade 3	14 (10.8)	6 (4.7)	20 (10.9)
Grade 4	0	2 (1.6)	2 (0.8)
Grade 5	2 (1.5)	0	2 (0.8)
AEs ≥ Grade 3	16 (12.3)	8 (6.3)	24 (9.3)

SAEs	8 (6.2)	3 (2.3)	11 (4.3)
AE leading to drug withdrawal	4 (3.1)	0	4 (1.6)
Fatal TEAEs	2 (1.5)	0	2 (0.8)

Source: FDA Clinical Reviewer

7.3.1 Deaths

Study CT-P10 3.3

As of a data cut-off of February 23, 2018, there were a total of 11 deaths in study CT-P10 3.3. Of these, seven occurred after discontinuation of study drug, and five of these seven were due to disease progression. There were four deaths that were due to TEAEs, three in the CT-P10 group and one in the Rituxan® group. A summary of the deaths due to adverse events is provided in the table below.

Table 28. Study CT-P10 3.3: Deaths due to Causes Other than Disease Progression - Up to 30 Days after Last Dose

Patient ID	Treatment Group	Adverse Event	Summary of Case
(b) (6)	CT-P10	Tumor Lysis Syndrome	74 year-old female who was treated with 1 cycle of CT-P10 plus CVP on experienced TEAE reported as tumor lysis syndrome two weeks after starting treatment, and died due to cardiac and renal failure on treatment Day 16. The patient had a history of coronary artery disease, cerebral atherosclerosis and hypertension prior to study enrollment. The causes of death was reported as cardiac and renal failure.
(b) (6)	CT-P10	Gastric Adenocarcinoma	71 year-old female developed gastric adenocarcinoma (secondary malignancy) that was detected on CT scan for tumor assessment 56 days after maintenance cycle 6 (18 months after starting treatment). The patient died 4 months later due to clinical deterioration.

(b) (6)	CT-P10	Hepatic Infiltration by carcinoma	74 year-old male developed fever, asthenia, nausea and jaundice 43 days after maintenance cycle 9 (24 months after starting treatment). Ultrasound of liver showed parenchyma with heterogeneous, nodular echostructure, consistent with neoplasm. Findings were suggestive of bile duct or pancreatic duct carcinoma. Patient died 7 days after diagnosis due to hepatic infiltration by carcinoma.
	Rituxan®	Respiratory tract infection	83 year-old male developed fever and dyspnea 43 days after maintenance cycle 6 (18 months after starting treatment). He was hospitalized for respiratory tract infection and developed fatal acute respiratory distress syndrome (ARDS).

Source: FDA Clinical Reviewer

Study CT-P10 3.4

There were two deaths in this study, both in the CT-P10 treatment group. A summary of these deaths is provided in the table below.

Table 29. Study CT-P10 3.4: Deaths Up to 30 Days after Last Dose

Patient ID	Treatment Group	Adverse Event	Summary of Case
(b) (6)	CT-P10	Myocardial infarction	76 year-old male experienced a fatal myocardial infarction 26 days after Induction Cycle 5. He was found deceased in his home.
	CT-P10	Respiratory failure	81 year-old female developed abdominal and flank pain 41 days after Induction Cycle 4. Hospitalized. Abdominal CT showed stable lymphoma as well as fibrotic and inflammatory changes of the lungs consistent with long-standing pulmonary fibrosis. While admitted, developed hypoxia and diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP). Patient died in the ICU due to respiratory failure secondary to BOOP.

Source: FDA Clinical Reviewer

7.3.2 Nonfatal Serious Adverse Events

Study CT-P10 3.3

A total of 21 (30%) subjects in the CT-P10 group and 13 (18.6%) in the Rituxan® group experienced at least one serious adverse event (SAE). The most common SAEs were lower respiratory tract infections, pneumonia and febrile neutropenia. An overview of the serious adverse events by preferred term is depicted in the table below.

Table 30. Study CT-P10 3.3 - Serious Adverse Events by Preferred Term

System Organ Class Preferred Term	CT-P10 N=70 n (%)	US-Rituxan® N=70 n (%)
Total number of TESAEs	36	21
Number (%) of patients with ≥ 1 TESA	21 (30.0)	13 (18.6)
Blood and lymphatic system disorders	4 (5.7)	4 (5.7)
Febrile neutropenia	2 (2.9)	3 (4.3)
Neutropenia	2 (2.9)	1 (1.4)
Leukopenia	0	1 (1.4)
Pancytopenia	1 (1.4)	0
Anemia	1 (1.4)	0
Cardiac disorders	1 (1.4)	1 (1.4)
Atrial fibrillation	1 (1.4)	0
Tachycardia	0	1 (1.4)
Gastrointestinal disorders	2 (2.9)	2 (2.9)
Constipation	1 (1.4)	0
Diarrhea	0	1 (1.4)
Ileus	0	1 (1.4)
Small intestinal perforation	1 (1.4)	0
Infections and infestations	7 (10.0)	5 (7.1)
Pneumonia	4 (5.7)	1 (1.4)
Lower respiratory tract infection	1 (1.4)	5 (7.1)
Abdominal infection	1 (1.4)	0
Appendicitis	1 (1.4)	0
Campylobacter gastroenteritis	1 (1.4)	0
Respiratory, thoracic and mediastinal disorders	3 (4.3)	1 (1.4)
Chronic obstructive pulmonary disease	2 (2.9)	1 (1.4)
Pleural effusion	1 (1.4)	0
Pulmonary embolism	1 (1.4)	0

Vascular disorders	2 (2.9)	2 (2.9)
Deep vein thrombosis	1 (1.4)	0
Hypertension	1 (1.4)	0
Peripheral ischemia	0	1 (1.4)
Thrombophlebitis	0	1 (1.4)

Source: FDA Clinical Reviewer

Study CT-P10 3.4

A total of 11 (4.3%) subjects experienced an SAE, 8 (6.2%) in the CT-P10 group and 3 (2.3%) in the Rituxan® group. The table below illustrates the serious adverse events by grade and preferred term that occurred in each treatment group.

Table 31. Study CT-P10 3.4 - Serious Adverse Events by Grade and Preferred Term

	CT-P10 N=130 n (%)	Rituxan® N=128 n (%)
Grade 5	2 (1.5)	0
Myocardial infarction	1 (0.8)	0
Respiratory failure	1 (0.8)	0
Grade 4	0	1 (0.8)
Acute kidney injury	0	1
Grade 3	5 (3.9)	1 (0.8)
Urinary tract infection	1 (0.8)	0
Squamous cell carcinoma of lung	1 (0.8)	0
Gastrointestinal surgery	1 (0.8)	0
Constipation	1 (0.8)	0
Abortion, spontaneous	1 (0.8)	0
Genital Prolapse	0	1 (0.8)
Grade 2	1 (0.8)	1 (0.8)
Chest discomfort	1 (0.8)	0
Pneumonia	0	1 (0.8)
TOTAL	8 (6.2)	3 (2.3)

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: In Study CT-P10 3.4, there were slightly more SAEs in the CT-P10 treatment group. However, the numbers were small and several of these were due to extraneous causes such as squamous cell carcinoma of the lung and gastrointestinal surgery.

7.3.3 Dropouts and/or Discontinuations

Study CT-P10 3.3

There were more subjects with at least one TEAE leading to permanent study drug discontinuation in the CT-P10 group vs. Rituxan® group (10.0% vs.7.1%). These events represented a spectrum of SOCs. These events are summarized in the table below.

Table 32. Study CT-P10 3.3 - TEAEs Leading to Permanent Study Drug Discontinuation

	CT-P10 N=70 n (%)	Rituxan® N=70 n (%)
Number of Patients With At Least One TEAEs Leading to Permanent Study Drug Discontinuation	7 (10.0)	5 (7.1)
Total Number of TEAEs Leading to Permanent Study Drug Discontinuation	7	5
Hypertension (Grade 3)	1	-
Infusion related reaction (Grade 2)	1	-
Post procedural fistula (Grade 2)	1	-
Liver function test abnormal (Grade 3)	1	-
Tumor lysis syndrome (Grade 5)	1	-
Adenocarcinoma gastric (Grade 5)	1	-
Prostate cancer (Grade 3)	1	-
Tuberculosis (Grade 2)	-	1
Febrile neutropenia (Grade 3)	-	1
Hepatitis B (Grade 2)	-	1
Lower respiratory tract infection (Grade 5)	-	1
Myeloproliferative disorder (Grade 1)	-	1

Source: FDA Clinical Reviewer

Study CT-P10 3.4

A total of 4 subjects discontinued treatment due to an adverse event in study CT-P10 3.4, all in the CT-P10 treatment group. No subjects in the Rituxan® group discontinued treatment due to an adverse event. These events are summarized in the table below.

Table 33. Study CT-P10 3.4 - TEAEs Leading to Permanent Study Drug Discontinuation

	CT-P10 N=130 n (%)	Rituxan® N=128 n (%)
Number of Patients With At Least One TEAEs Leading to Permanent Study Drug Discontinuation	4 (3.1)	0
Total Number of TEAEs Leading to Permanent Study Drug Discontinuation	4	0
Squamous cell carcinoma of lung (Grade 3)	1	-
Myocardial infarction (Grade 5)	1	-
Dermatitis atopic (Grade 2)	1	-
Respiratory failure (Grade 5)	1	-

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: *There did not appear to be a clinically significant pattern among the observed treatment-emergent adverse events leading to study drug discontinuation in either study.*

7.3.4 Significant Adverse Events

See Sections 7.3.2, 7.3.3 and 7.3.5

7.3.5 Submission Specific Primary Safety Concerns

Major events of special interest that are listed as Warnings and Precautions in the US-Rituxan® label include infections, infusion reactions, cardiac adverse reactions and severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML).

Infusion-Related Reactions (IRRs)

An overview of the incidence of infusion-related reactions (IRRs) that occurred in studies CT-P10 3.3 and CT-P10 3.4 is provided in the table below.

Table 34. Studies CT-P10 3.3 and CT-P10 3.4: Adverse Event of Special Interest - Infusion-Related Reactions (IRR)

	Study CT-P10 3.3		Study CT-P10 3.4	
	CT-P10 N=70 n(%)	Rituxan® N=70 n(%)	CT-P10 N=130 n(%)	Rituxan® N=128 n(%)
Number of Events	25	25	47	43
Number (%) of patients with ≥1 IRR	16 (22.9)	19 (27.1)	40 (30.8)	37(28.9)
Grade 1 (mild)	4 (5.7)	6 (8.6)	4 (3.1)	2 (1.6)
Grade 2 (moderate)	10 (14.3)	14 (20.0)	35 (26.9)	35 (27.3)
Grade 3 (severe)	2 (2.9)	0	1 (0.8)	1 (0.8)
Number (%) of patients with ≥1 IRR leading to discontinuation	1 (1.4)	0	0	0
Number (%) of patients with ≥1 IRR requiring any treatment	13 (18.6)	18 (25.7)	36 (27.7)	29 (22.7)

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: Infusion-related reactions occurred in both studies, the majority of which were moderate in severity. There were no meaningful differences in the incidence or severity of IRRs between CT-P10 and Rituxan®.

Infections

An overview of the infections that occurred in studies CT-P10 3.3 and CT-P10 3.4 is provided in table 35 and 36, respectively.

Table 35. Study CT-P10 3.3: Adverse Event of Special Interest – Infections and Infestations

	Study CT-P10 3.3	
	CT-P10 N=70 n(%)	Rituxan® N=70 n(%)
Infections and Infestations	31 (44.3)	32 (45.7)
Upper respiratory tract infection	13 (18.6)	18 (25.7)
Urinary tract infection	6 (8.6)	6 (8.6)
Lower respiratory tract infection	6 (8.6)	4 (5.7)
Pneumonia	6 (8.6)	3 (4.3)
Fungal infection	2 (2.9)	4 (5.7)
Influenza	2 (2.9)	4 (5.7)
Localized infection	3 (4.3)	3 (4.3)
Sinusitis	4 (5.7)	2 (2.9)
Herpes virus infection	3 (4.3)	1 (1.4)

Source: FDA Clinical Reviewer

Table 36. Study CT-P10 3.4: Adverse Event of Special Interest – Infections and Infestations

	Study CT-P10 3.4	
	CT-P10 N=130 n(%)	Rituxan® N=128 n(%)
Infections and Infestations	35 (26.9)	27 (21.1)
Herpes virus infection	5 (3.8)	0
Lower respiratory tract infection	0	3 (2.3)
Upper respiratory tract infection	16 (12.3)	14 (10.9)
Urinary tract infection	5 (3.8)	6 (4.7)
Pneumonia	2 (1.5)	1 (0.8)
Sinusitis	1 (0.8)	1 (0.8)

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: Infections occurred more frequently in study CT-P10 3.3, likely related to the more severe patient population (advanced follicular lymphoma vs. low tumor burden follicular lymphoma), as well as the concomitant use of CVP chemotherapy. There were no clinically meaningful differences in the incidence of infections between the two treatment groups in either study.

Cardiac Disorders

An overview of cardiac disorders that occurred in studies CT-P10 3.3 and CT-P10 3.4 is provided in the table below.

Table 37. Studies CT-P10 3.3 and CT-P10 3.4: Adverse Event of Special Interest – Cardiac Disorders

	Study CT-P10 3.3		Study CT-P10 3.4	
	CT-P10 N=70 n(%)	Rituxan® N=70 n(%)	CT-P10 N=130 n(%)	Rituxan® N=128 n(%)
Cardiac Disorders	4 (5.7)	7 (10.0)	7 (5.4)	3 (2.3)
Cardiac failure	1 (1.4)	2 (2.9)	-	-
Atrial fibrillation	2 (2.9)	-	1 (0.8)	1 (0.8)
Palpitations	1 (1.4)	1 (1.4)	1 (0.8)	-
Bradycardia	-	1 (1.4)	2 (1.5)	1 (0.8)
Tachycardia	-	1 (1.4)	1 (0.8)	-
Myocardial ischemia	-	1 (1.4)	-	-
Supraventricular extrasystoles	-	1 (1.4)	-	1 (0.8)
Mitral valve incompetence	-	-	1 (0.8)	-
Myocardial infarction	-	-	1 (0.8)	-

Source: FDA Clinical Reviewer

Other Adverse Events of Special Interest

- There were no cases of severe mucocutaneous reactions (Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis, etc.) in studies CT-P10 3.3 or CT-P10 3.4.
- Hepatitis B reactivation: One subject ((b) (6) in study CT-P10 3.3 (Rituxan® treatment group) developed HBV reactivation, which was asymptomatic and did not result in liver impairment or other clinical sequelae. No subjects in study CT-P10 3.4 developed hepatitis B reactivation.
- There were no cases of PML in either study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CT-P10 3.3

Overall, the majority of subjects in both treatment groups experienced at least one treatment-emergent adverse event.

A total of 63 (90.0%) and 60 (85.7%) patients experienced one or more TEAE in the CT-P10 and Rituxan treatment groups, respectively. The most common adverse events in both treatment groups were neutropenia, infusion related reactions, upper respiratory infections and constipation. A summary of TEAEs that occurred in at least 10% of patients in either treatment group is provided in the table below.

Table 38. Study CT-P10 3.3: Summary of TEAEs (≥10% of Patients in Either Treatment Group)

Preferred Term	CT-P10 N=70 n (%)	Rituxan® N=70 n (%)
Number (%) of patients with ≥ 1 TEAE	63 (90.0)	60 (85.7)
Neutropenia	28 (40.0)	20 (28.6)
Infusion related reaction	16 (22.9)	19 (27.1)
Upper respiratory infection	10 (14.3)	12 (17.1)
Constipation	12 (17.1)	10 (14.3)
Peripheral sensory neuropathy	7 (10.0)	9 (12.9)
Alopecia	10 (14.3)	6 (8.6)
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	4 (5.7)	7 (10.0)
Arthralgia	7 (10.0)	4 (5.7)
Nasopharyngitis	3 (4.3)	7 (10.0)

Source: FDA Clinical Reviewer

Study CT-P10 3.4

A total of 92 (70.8%) and 86 (67.2%) patients experienced one or more TEAE in the CT-P10 and Rituxan treatment groups, respectively. The most common adverse reactions in both groups were infusion related reactions, fatigue, diarrhea and upper respiratory tract infections. A summary of TEAEs that occurred in at least 3% of patients in either treatment group is provided in the table below.

Table 39. Study CT-P10 3.4: Summary of TEAEs (≥3% of Patients in Either Treatment Group)

Preferred Term	CT-P10 N=130 n (%)	Rituxan® N=128 n (%)
Number (%) of patients with ≥ 1 TEAE	92 (70.8)	86 (67.2)
Infusion related reaction	40 (30.8)	37 (28.9)
Fatigue	9 (6.9)	12 (9.4)
Diarrhea	8 (6.2)	6 (4.7)
Upper respiratory tract 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)
Stomatitis	1 (0.8)	4 (3.1)

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: In study CT-P10 3.3, more subjects in the CT-P10 treatment group experienced neutropenia (40.0% vs. 28.6%). However, this may be explained by the difference in bone marrow involvement at baseline between the two treatment groups. In study CT-P10 3.3, a total of 45 (64.3%) patients in the CT-P10 treatment group had bone marrow involvement at baseline, compared to 33 (47.1%) in the Rituxan® treatment group. This difference in neutropenia was not reproduced in study CT-P10 3.4. The remainder of adverse events were similar in the two treatment groups in both studies.

7.4.2 Laboratory Findings

Laboratory evaluations were obtained at regular intervals in studies CT-P10 3.3 and CT-P10 3.4. As expected with rituximab treatments, decreases from baseline in mean B-cell count in each treatment group were observed in both clinical studies. For all hematology, clinical chemistry and urinalysis parameters, the mean changes from baseline in both studies were small and there were no notable differences between the treatment groups.

A summary of patients with CTCAE Grade 3 or higher laboratory abnormalities in studies CT-P10 3.3 and CT-P10 3.4 is provided in the table below.

Table 40. Studies CT-P10 3.3 and CT-P10 3.4: Incidence of Grade ≥3 Laboratory Abnormalities

	Study CT-P10 3.3		Study CT-P10 3.4	
	CT-P10 N=70 n(%)	Rituxan® N=70 n(%)	CT-P10 N=130 n(%)	Rituxan® N=128 n(%)
Alanine aminotransferase increased				
Grade 3	3 (4.3)	0	1 (0.8)	0
Alkaline phosphatase increased				
Grade 3	1 (1.4)	0	0	0
Hyperkalemia				
Grade 3	0	0	0	2 (1.6)
Hypernatremia				
Grade 3	1 (1.4)	0	0	0
Hyperuricemia				
Grade 4	1 (1.4)	3 (4.3)	0	1 (0.8)
Hypoalbuminemia				
Grade 3	1 (1.4)	1 (1.4)	0	0
Hypocalcemia				
Grade 3	0	1 (1.4)	1 (0.8)	0
Grade 4	1 (1.4)	0	0	0
Hypokalemia				
Grade 3	0	1 (1.4)	1 (0.8)	0
Grade 4	1 (1.4)	1 (1.4)	0	0
Hyponatremia				
Grade 3	1 (1.4)	1 (1.4)	1 (0.8)	2 (1.6)
Neutrophil count decreased				
Grade 3	14 (20.0)	9 (12.9)	5 (3.8)	3 (2.3)
Grade 4	5 (7.1)	5 (7.1)	0	0
White blood cell decreased				
Grade 3	6 (8.6)	6 (8.6)	1 (0.8)	0

Source: FDA Clinical Reviewer

Clinical Reviewer Comment: *In study CT-P10 3.3, more subjects in the CT-P10 treatment group the Grade 3 adverse event of “Neutrophil count decreased” (20.0% vs. 12.9%). However, this may be explained by the difference in bone marrow involvement at baseline between the two treatment groups. This difference in Grade 3 neutropenia was not reproduced in study CT-P10 3.4. The remainder of Grade ≥3 laboratory adverse events were similar in the two treatment groups in both studies.*

7.4.3 Vital Signs

Vital signs (including blood pressure, heart rate, respiratory rate and temperature) were measured at every visit in studies CT-P10 3.3 and CT-P10 3.4. Vital sign measurements were also monitored during the study treatment infusion as part of the monitoring for hypersensitivity reactions. There were no notable differences observed between the treatment groups in study CT-P10 3.3 or study CT-P10 3.4.

7.4.4 Electrocardiograms (ECGs)

ECGs were collected at each scheduled visit and one hour after the end of each infusion of study drug. All ECG findings were classified as either “Normal”, “Abnormal, not clinically significant”, or “Abnormal, clinically significant”. There were no notable differences observed between the treatment groups in study CT-P10 3.3 or study CT-P10 3.4.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies for similarity of safety endpoints that were submitted for review.

7.4.6 Immunogenicity

See Clinical Pharmacology review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

There were no clinically meaningful differences in safety based on demographic factors, including age, gender and race in either study. The table below summarizes the frequency of treatment-emergent adverse events by age, gender and race.

Table 41. Summary of TEAEs by Age, Gender and Race

		Study CT-P10 3.3		Study CT-P10 3.4	
		CT-P10 N=70 n(%)	Rituxan® N=70 n(%)	CT-P10 N=130 n(%)	Rituxan® N=128 n(%)
Age	<65	46/51 (90.2)	40/49 (81.6)	64/84 (76.2)	59/90 (65.6)
	≥65	17/19 (89.5)	20/21 (95.2)	28/46 (60.9)	27/38 (71.1)
Gender	Male	26/30 (86.7)	28/33 (84.8)	41/66 (62.1)	35/57 (61.4)
	Female	37/40 (92.5)	32/37 (86.5)	51/64 (79.7)	51/71 (71.8)
Race	White	45/51 (88.2)	42/52 (80.8)	52/77 (67.5)	46/75 (61.3)
	Asian	11/11 (100.0)	13/13 (100.0)	37/47 (78.7)	38/49 (77.6)
	Other	7/8 (87.5)	5/5 (100.0)	3/6 (50.0)	2/4 (50.0)

Source: Summary of Clinical Safety, Table 2.7.4-70

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

No drug interaction studies have been conducted with CT-P10.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

No human or animal studies have investigated the potential effects of CT-P10 during pregnancy and lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

No human studies have investigated the potential effects of CT-P10 in pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No data from clinical trials available.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

To date, CT-P10 is approved in 43 countries worldwide. Per the Applicant, review of safety data from the marketed use of CT-P10 did not reveal any new safety issues. There is one post-marketing surveillance (PMS) study for rituximab currently being conducted in South Korea.

9 Appendices

9.1 Literature Review/References

1. NCI SEER Program, Cancer Stat Facts: Non-Hodgkin Lymphoma, Available at <https://seer.cancer.gov/statfacts/html/nhl.html>, Accessed October 17, 2018.
2. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*, 2005. 105(4):1417-1423.
3. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi, *J Clin Oncol*. 2013, 31(12):1506-1513.
4. Ardeschna KM, Smith P, Norton A et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomized controlled trial. *Lancet Oncol*. 2003, 362(9383):516-22.

9.2 Labeling Recommendations

Labeling review and discussions are still ongoing at the time of this review.

9.3 Advisory Committee Meeting

An Oncology Drug Advisory Committee (ODAC) meeting was held on October 10, 2018. The purpose of the ODAC meeting was to discuss whether the totality of evidence presented support licensure of CT-P10 as a biosimilar to US-licensed 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 were no clinically meaningful differences between CT-P10 and US-Rituxan® in terms of the safety, purity and potency of the product.

The Agency presented the following discussion questions to the Committee:

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. Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan®.
3. Please discuss whether there is adequate justification to support licensure for the proposed indications sought by the Applicant.

The Agency presented the following voting question to the committee:

Does the totality of the evidence presented support licensure of CT-P10 as a biosimilar to US-licensed Rituxan for the following indications:

Treatment of adult patients with Non-Hodgkin's Lymphoma (NHL)

- Relapsed or refractory, low grade or follicular, CD20+ B-cell NHL as a single agent
- Previously untreated follicular, CD20+, 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+, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine and prednisone (CVP) chemotherapy.

Members of the ODAC agreed that the analytical data presented by the Applicant and the Agency supported the criterion that CT-P10 is highly similar to US-licensed Rituxan®, notwithstanding minor differences in clinically inactive components. The committee was in consensus that the clinical trials presented no evidence to suggest a clinically meaningful difference between US-licensed Rituxan® and CT-P10.

Clinical and Statistical Review
Rachel Ershler, MD
Xin Gao, PhD
BLA 761088
CTP-10 (Truxima)

Vote Result: YES: 16 NO: 0 ABSTAIN: 0

The committee unanimously agreed that the totality of analytical, pharmacologic, immunogenicity and clinical evidence supported the licensure of CT-P10 for all three proposed indications based on the high degree of similarity, except for minor components, between CT-P10 and US-licensed Rituxan®.

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/

RACHEL E ERSHLER
10/25/2018

XIN GAO
10/25/2018

VISHAL BHATNAGAR
10/25/2018

YUAN L SHEN
10/25/2018

Cross Discipline Team Leader Review

Clinical Pharmacology	Sarah Schrieber, Pharm.D.
Office of Scientific Investigations/ Division of Clinical Compliance Evaluation	Min Lu, MD, MPH; Janice Pohlman, MD, MPH; Kassa Ayalew MD, MPH

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 are as follows:

- Non-Hodgkin's Lymphoma (NHL)

(b) (4)

The proposed dosing regimens, which are the same as US-licensed Rituxan are as follows:

- The dose for NHL is 375 mg/m².

(b) (4)

2. Background

Source: Derived in part from the reviews by Drs. Shah, Manning, Travis and Freeman

Rituximab is a chimeric murine/human monoclonal antibody that binds the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. After binding to CD20 on the cell surface, rituximab is believed to 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 a 3-way analytical similarity assessment of CT-P10, Rituxan, and MabThera, including 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 results of the 3-way analytical similarity assessment support establishment of a scientific bridge between CT-P10, Rituxan, and MabThera.

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.

CT-P10 was approved in South Korea in November 2016, and 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 abbreviated nonclinical and clinical programs.

3. CMC/Device

Source: Derived in part from the CMC Executive Summary Review.

CT-P10 is produced in genetically engineered CHO ^{(b) (4)} cells. CT-P10 drug product, Truxima, is manufactured to the same concentration, formulation, and presentation as U.S.-licensed Rituxan. Truxima 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 at 100 mg/10 mL or 500 mg/50 mL.

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761088 for TRUXIMA manufactured by Celltrion, Inc. The data submitted in the application are not sufficient to support a conclusion that the manufacture of TRUXIMA is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, the Office of Biotechnology Products (OBP)/OPQ is recommending a Complete Response letter be issued to Celltrion to outline the deficiencies and the information and data that will be required to support approval.

From an immunogenicity perspective, the immunogenicity assays are not sufficiently sensitive to detect anti-drug antibodies (ADA) and neutralizing antibodies (NAb) in presence of CT-P10 at plasma concentrations observed in patients with Advanced Stage Follicular Lymphoma (AFL). Although the insufficiently-sensitive assays rendered the immunogenicity results in patients with AFL unreliable, we do not believe that an immunogenicity assessment in these patients would yield potentially meaningful data. The Division of Hematology Products and the Division of Pulmonary, Allergy and Rheumatology Products agree that such an assessment in patients with AFL is not necessary because the rheumatoid arthritis population is the appropriate population for evaluating immunogenicity in this case. The assays are acceptable for testing of ADAs and NABs in the samples from patients with rheumatoid arthritis.

Per Division of Inspectional Assessment (DIA)/OPF/OPQ, the application cannot be approved during this review cycle due to facility deficiencies. A pre-license inspection of TRUXIMA 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 Celltrion. The Division of Inspectional Assessment, OPF, OPQ is recommending a withhold status, and a Complete Response letter be issued to Celltrion.

The Division of Microbiology Assessment/ OPF/OPQ is recommending a Complete Response letter be issued to Celltrion.

From an analytical similarity perspective, OBP/OPQ has determined that the analytical similarity data as presented in the BLA is acceptable to support the conclusions that:

- The biological product, CT-P10, is highly similar to U.S.-licensed Rituxan,
- A sufficient scientific bridge was established to support the use of E.U.-approved MabThera as a comparator in clinical studies supporting this application.

4. Nonclinical Pharmacology/Toxicology

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

The results of the in vitro 3-way similarity assessment, the tissue cross-reactivity study, and the comparative repeat-dose toxicity study in cynomolgus monkeys support the

demonstration of biosimilarity between CT-P10 and Rituxan. From the perspective of nonclinical pharmacology and toxicology, CT-P10 may be approved for the proposed indications.

5. Clinical Pharmacology/Biopharmaceutics

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

The applicant submitted pharmacokinetic (PK) similarity data that was contained within the comparative clinical study in patients with Rheumatoid Arthritis (RA) to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan (Study CT-P10 3.2) in patients with RA. Part 1 of Study CT-P10 3.2 was a randomized, controlled, double-blind, 3-arm parallel study to compare the PK of 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-last} , AUC_{0-inf} and AUC_{0-14} 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.

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 in patients with RA.

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.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Derived in part from the DHP Clinical Review by Dr. Shah; the Statistical Review by Drs. Ye, Nie, and Gwise; and the DPARP Division Review by Drs. Travis, Abugoy, Freeman, MD; Nikolov, and Chowdhury.

The Table below includes the studies conducted in rheumatologic indications.

Table 1. Studies in patients with RA

Study ID	Design	Objective/Duration	Treatment	Total Number (randomization) Arms: # per Arm
Main Study in RA (Commercial Drug Product Manufacturing Drug Processes C and D)				
CT-P10 3.2	R, C, DB, PG	<u>Part 1</u>: 3-way PK similarity between CT-P10, Rituxan and MabThera (24 weeks) <u>Part 2</u>: CCS between CT-P10 and the combined reference products (Rituxan and MabThera) (up to week 48). Efficacy assessed by change from baseline in DAS28 (CRP) at Week 24. <u>Part 3</u>: Extension period with single transition for safety and immunogenicity (up to 76 weeks)	CT-P10, US-Rituxan or MabThera (1000 mg) co-administered with MTX (7.5-25 mg/week); up to 2 courses* in the Main study (parts 1 and 2) and 1 additional course* in the extension portion.	<u>Part 1</u>: N=189 (1:1:1) • CT-P10: 64 • EU-Mab Thera: 65 • US-Rituxan: 60 <u>Part 2</u>: N=372 patients (includes patients from Part 1) • CT-P10: 161 • EU-Mab Thera: 60 • US-Rituxan: 151 <u>Part 3</u> (Extension): N=295 • CT-P10 continued: 122 • US-Rituxan continued: 64 • US-Rituxan→CT-P10: 62 • EU-MabThera→CT-P10: 47
Supportive Studies in RA (Non-commercial Drug Product Manufacturing Process B)				
CT-P10 1.1	R, C, PG, DB	PK similarity between CT-P10 and EU-MabThera (AUC, Cmax) up to Week 24. Evaluate additional PK variables, long-term efficacy and safety up to Week 72.	CT-P10 or MabThera 1000 mg co-administered with MTX (10-25 mg/week), up to 2 courses* of treatment	N= 154 (2:1) CT-P10: 103 EU-MabThera: 51
CT-P10 1.3	OL, single-arm Extension	Extension study to CT-P10 1.1 Long-term safety (up to 104 weeks)	CT-P10 (1000 mg) co-administered with MTX (10-25 mg/week), up to 2 courses* of treatment	N= 58 CT-P10 continued: 38 MabThera→CT-P10: 20
R: randomized, C: controlled, DB: Double-blind, OL: open-label, PG: parallel group *each course of treatment consists of 2 infusions with a 2-week interval				

Source: DPARP Division Review

In Study CT-P10 3.2, the primary endpoint, change from baseline in DAS28 (CRP) at week 24 was analyzed using an analysis of covariance (ANCOVA) which included treatment, study part, sex, region, race, reason for discontinuing prior anti-TNF therapy, and screening RF or anti-CCP status as factors. Since the randomization was modified between parts 1 and 2 of the study, the Agency requested that the Applicant additionally include a treatment by interaction term to the model. The Applicant’s primary analysis included only patients who completed the Week 24 visit.

CT-P10 met the pre-specified similarity margin. The DPARP statistical review team notes that the Applicant’s primary analysis excluded patients who failed to complete the study, which the Agency did not believe is appropriate. However, revised tipping point analyses, intended to

address this limitation, confirm that the conclusions are robust in the face of missing data, with implausible assumptions required to reverse the conclusion of biosimilarity.

Similarity of CT-P10 to the combined comparator products is further supported by analyses of DAS28 (ESR), individual components of DAS28, and ACR- 20, 50 and 70 response rates. The analyses showed a relatively small difference between the CT-P10 treatment and comparator treatment arms compared to overall changes from baseline. Further, the analyses of ACR20 response rates met a similarity margin of $\pm 12\%$, which is within the FDA-recommended margin for similarity when this endpoint is used as a primary endpoint in comparative clinical studies in RA.

Overall, the DPARP statistical review team concluded that the results from the comparative clinical study 3.2 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.

From a DPARP clinical perspective, the submitted clinical data in RA are adequate to:

- 1) Support the demonstration of PK similarity between CT-P10 and US-licensed Rituxan.
- 2) Establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved MabThera to support the demonstration of biosimilarity of CT-P10 to US-licensed Rituxan.
- 3) Support a demonstration that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of safety, purity, and potency in the indication studied.
- 4) Support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to CT-P10 based on the similar safety or immunogenicity profile between patients undergoing a single transition from US-licensed Rituxan or EU-approved MabThera to CT-P10 as compared to those who continued treatment with comparator product.

5) (b) (4)

The Table below includes studies conducted in hematologic indications.

Table 2. Studies in Hematologic Indications

Study	Design	Population	N	Status	Cut-off (BLA)
Trials to Support Safety and Efficacy					
CT-P10 3.3	Phase 1/3 randomized	Advanced Follicular Lymphoma	Enrolled: 140 Part 1 Enrolled and randomized: 121 CT-P10: 59 Rituxan: 62 Part 2 Enrolled and randomized: 140 (including 121 from Part 1) CT-P10: 70 Rituxan: 70	Ongoing	27 June 2016
				(b) (4)	Terminated
Additional Trials to Support Safety					
CT-P10 3.4	Phase 3 randomized	Low Tumor Burden Follicular Lymphoma	216 (safety population)	Ongoing	-
Trials to Support Clinical Pharmacology (PK)					
CT-P10 3.2	Phase 3 randomized	Rheumatoid Arthritis	372 (Main Study Period) 295 (Extension Study Period)	Completed	-

Source: DHP Clinical Review

In Part 2 of study CT-P10 3.3, the primary endpoint was objective response rate (ORR) compared between CT-P10 and US-licensed Rituxan arms. The study was not designed to show equivalence. The study was designed to show non-inferiority of CT-P10 compared to US-licensed Rituxan, even though the study was under-powered for the pre-specified non-inferiority margin of 7%. The observed ORR difference between the arms was 5.7% and the 90% confidence interval was [-1.7%, 14.7%]. The lower 90% confidence interval of observed difference in ORR was greater than the pre-specified non-inferiority margin of 7%. Therefore, the primary objective was met for non-inferiority of ORR. However, the 90% upper bound of the difference does not rule out non-superiority. The time-to-event secondary endpoints were not available at the data cut-off because the data were not mature.

From the DHP clinical and statistical perspective, there were concerns that the results of the clinical study CT-P10 3.3 may not provide support of a demonstration of no clinically meaningful differences between CT-P10 and the reference product Rituxan for the targeted oncology population. The difference observed in ORR between CT-P10 and Rituxan create uncertainty as to whether there are no clinically meaningful differences between CT-P10 and Rituxan. Celltrion did not provide adequate information and justification to resolve this uncertainty. It was decided that this application should be presented to the Oncology Drug Advisory Committee (ODAC) to address this and other concerns with the application.

8. Safety

Source: Derived in part from the DHP Clinical Review by Dr. Shah and the DPARP Division Review by Drs. Travis, Abugoy, Freeman, MD; Nikolov, and Chowdhury.

The DPARP Clinical safety review was primarily based on the clinical safety data from patients with rheumatoid arthritis treated on Study CT-P10 3.2, which enrolled 372 patients. No new safety signals were identified in the CT-P10 group compared to the known adverse event profile of US-licensed Rituxan. Overall, there were no major differences in adverse events (AE), serious adverse events (SAE), or AEs leading to discontinuations between the treatment groups. The total number of treatment emergent adverse events (TEAE) was higher in the CT-P10 arm (77.6%) than in the US-licensed Rituxan (64.2%) or EU-approved MabThera (65.0%) in the Main study Period of study 3.2 with an increase in the number of infusion related reactions. The nature and severity of the infusion related reactions are similar across treatment groups and are consistent with known safety profile of US-licensed Rituxan. Other adverse events of special interest (AESI) were generally similar across treatment arms. Infections were the most common adverse event in all treatment groups and no difference was seen in infections between treatment groups. One death was reported in the Study 3.2 Main Study Period.

The DHP clinical safety review was primarily based on review of data from Study CT-P10 3.3, a phase 1/3, randomized, parallel-group, active-controlled, double-blind study to demonstrate equivalence of PK and noninferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with CVP in patients with advanced follicular lymphoma. There were 70 patients in each arm of the study (N=140).

Key safety findings from Study CT-P10 3.3, and from the supportive safety database:

- Deaths: There was 1 death (1 in the CT-P10 group and 0 in the Rituxan group) within 30 days of study treatment attributable to tumor lysis syndrome.
- Serious Adverse Events (SAEs) and Discontinuations: Overall, SAEs were more common in CT-P10 group. These were more frequent in the CT-P10 group across a number of SOCs. Compared with Rituxan (12.9%), 22.9% patients experienced at least one SAE. There were more patients with at least one TEAE leading to permanent study drug discontinuation in the CT-P10 group vs. Rituxan group (7.1% vs. 1.4%).
- Grade 3 and 4 Adverse Reactions: At the preferred term level, Grade 3 or higher TEAEs were more frequent in the CT-P10 group. Twenty-six (37.1%) and 20 (28.6%) patients experienced one or more Grade 3 or higher TEAE in the CT-P10 and Rituxan arms, respectively. Notably, Grade 3 or higher neutropenia was more frequent in the CT-P10 group (25.7% vs. 15.7% Rituxan group) as was pneumonia (5.7% vs 0% in the Rituxan group).
- Common Adverse Reactions: In Study CT-P10 3.3, the common preferred term level TEAEs (i.e., $\geq 3\%$ of patients) in the CT-P10 arm were Neutropenia (34.3%), infusion related reaction (22.9%), constipation (17.1%), neuropathy peripheral (14.3%), and alopecia (14.3%). The most frequently reported TEAEs in the Rituxan arm were infusion related reaction (24.3%), neutropenia (22.9%), upper respiratory tract infection (17.1%), and neuropathy peripheral (17.1%).

In Study CT-P10 3.3, there was a higher incidence of SAEs, 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 create uncertainty as to whether there are no clinically meaningful differences between CT-P10 and Rituxan, and Celltrion has not provided adequate information and justification to resolve these uncertainties.

9. Advisory Committee Meeting

It was intended that this BLA would be presented to the Oncologic Drugs Advisory Committee (ODAC); however, the facility issues precluded a presentation to the ODAC.

10. Pediatrics

The Applicant submitted their agreed upon Initial Pediatric Study Plan with the BLA. Waivers were requested (b) (4)



11. 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 and CT-P10 3.3. No investigators or sub-investigators declared financial interests.
- **Other GCP issues:** None.
- **OSI audits:** 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.

There were no other outstanding regulatory issues.

12. Labeling

Labeling negotiations were not conducted as it was assessed that this application would receive a Complete Response.

13. Recommendations

- Recommended Regulatory Action: Complete Response

The OPQ and DHP Clinical and Statistical teams recommended a Complete Response. Please refer to the CR letter for a complete list of deficiencies and comments that will be communicated to the Applicant. The Clinical Deficiency to be communicated to the Applicant is below:

You have not provided adequate information and scientific justification that Study CT-P10 3.3, in patients with advanced follicular lymphoma, is adequate to detect differences between the products, should they exist, to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of the safety, purity, and potency of the product. You will need to provide additional information and justification to address the uncertainty raised by observed differences, specifically in objective response rate (ORR) and adverse events, in Study CT-P10 3.3.

Based on the above, I recommend a Complete Response for BLA 761088 for Truxima, a proposed biosimilar to U.S.-licensed Rituxan.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not Applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not Applicable.

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/s/

NICOLE J GORMLEY
02/28/2018

CLINICAL REVIEW

Application Type Original 351(k)
Application Number(s) BLA 761088
Priority or Standard Standard

Submit Date(s) 28 April 2017
Received Date(s) 28 April 2017
BsUFDA Goal Date 28 February 2018
Division / Office Division of Hematology Products/
Office of Hematology and
Oncology Products

Reviewer Name(s) Anand Shah
Review Completion Date 13 October 2017

Established Name CT-P10
(Proposed) Trade Name TRUXIMA
Therapeutic Class Chimeric murine/human
monoclonal antibody directed
against the CD20 antigen
Applicant Celltrion

Formulation(s) Injection (intravenous infusion)
Dosing Regimen Dose for NHL is 375 mg/m²

Indication(s) NHL,
Intended Population(s) NHL,

(b) (4)

(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Biologics License Application (BLA) 761088 was submitted by Celltrion, Inc. for CT-P10 (TRUXIMA) under section 351(k) of the Public Health Service Act. CT-P10 is a proposed biosimilar to US-licensed Rituxan. Comprehensive review of this BLA is still underway at the time of this clinical oncology review, but potential deficiencies were identified in the inspectional process; immunogenicity assessments; and in the clinical data submitted to support a demonstration of no clinically meaningful differences between CT-P10 (TRUXIMA) and US-licensed Rituxan. Therefore, from a clinical oncology perspective, I recommend an issuance of a complete response letter for CT-P10 (TRUXIMA) as a proposed biosimilar to Rituxan.

1.2 Risk Benefit Assessment

At the time of this review, there are substantial inspectional issues that may impact our conclusions regarding integrity of the analytic data. In addition, there are uncertainties related to the immunogenicity assays. It is therefore not possible to make an adequate assessment of the risk benefit profile of CT-P10 (TRUXIMA) as a proposed biosimilar to US-licensed Rituxan.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

Non-Hodgkin's Lymphoma is the most common hematological malignancy in adults, with B-cell lymphomas comprising more than 80% of all NHLs. In 2017, it is estimated there will be more than 72,000 new cases of NHL including greater than 20,000 deaths and more than 62,000 new cases of leukemia (all types) including over 24,000 deaths (1). Since its U.S. approval in 1997, rituximab is widely considered to be a substantial advancement in the management of these malignancies. Multiple clinical studies have demonstrated the favorable impact of rituximab on treatment, survival, and long-term outcomes of patients with NHL and leukemia. There are currently no approved U.S. biosimilars to Rituxan.

2.1 Product Information

Proper Name: TRUXIMA

Established Name: CT-P10

Dosage Forms: Injection: 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial

Chemical Class: Proposed biosimilar to Rituxan

Pharmacologic Class: B-lymphocyte antigen CD20 inhibitor

Mechanism of Action: CT-P10 is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab products mediate B-cell lysis.

Proposed Indication (Hematology / Oncology):

- Non-Hodgkin's Lymphoma (NHL)

(b) (4)

Dosage and Administration:

- Dose for NHL is 375 mg/m²

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Summary of Treatments Relevant to Proposed Indication

Drug	Approval Date
Rituxan (rituximab)	26 November 1997

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

CT-P10 (TRUXIMA) is not marketed in the U.S.

The reference product Rituxan was approved in 1997 and is currently marketed in the U.S. for the following indications:

- Non-Hodgkin's Lymphoma (NHL)
- Chronic Lymphocytic Leukemia (CLL)

- 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 (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids

2.4 Important Safety Issues With Consideration to Related Drugs

The Rituxan (b) (4) Prescribing Information list the following adverse reactions:

Rituxan

Most common (NHL): infusion reactions, fever, lymphopenia, chills, infection and asthenia

Most common (CLL): infusion reactions and neutropenia

(b) (4)

Rituxan

Tumor lysis syndrome, infections, cardiac arrhythmias and angina, bowel obstruction and perforation, live virus vaccines, cytopenias

(b) (4)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

March 19, 2014: BPD Type 2 Meeting (PIND 120885) to discuss development of CT-P10 as 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 registration 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.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

BLA 761088 was received 28 April 2017 as an electronic submission in eCTD format. No clinical issues were identified during the filing review.

Reviewer Comment: The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the applicant throughout the review process were addressed in a timely fashion.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies in the CT-P10 (TRUXIMA) biosimilar clinical development program were conducted in compliance with Good Clinical Practice. Office of Scientific Investigations (OSI) audits was still ongoing at the time of this review.

As per the Applicant, two GCP non-compliant sites (Site #4409 in Study CT-P10 3.2 and Site #2804 in Study CT-P10 3.3) were identified and closed due to scientific misconduct and serious GCP non-compliance. Instances of non-compliance included failure to conduct the study in accordance with ICH/GCP, failure to guarantee that only eligible subjects were randomized, inadequacies related to attributable, legible, contemporaneous, original and accurate (ALCOA) principles, and failure to follow protocol requirements for investigational product storage and administration. The patients enrolled at these sites were excluded from all analysis populations except for the sensitivity analysis for the primary PK endpoint for Study CT-P10 3.3, where they were included.

Reviewer Comment: All analyses in this review excluded subjects at the two sites cited above.

3.3 Financial Disclosures

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the Applicant requested statements of financial interests from a total of 179 Principal Investigators and 462 sub-investigators for the following studies:

- CT-P10 1.1
- CT-P10 1.3
- CT-P10 3.2
- CT-P10 3.3

As of 24 Mar 2017, a total of 641 financial disclosures for the investigators who participated in these trials were received. There were no principal or sub-investigators who did not return the financial disclosure information. No investigators had financial information to disclose

Reviewer Comment: There were no substantial issues related to financial disclosures in the course of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

At the time of completion of this review, only preliminary reports of significant issues were available from other review disciplines. Please also refer to separate to separate Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) review of CT-P10 for rheumatologic indications.

4.1 Chemistry Manufacturing and Controls

Please refer to separate CMC review.

4.2 Clinical Microbiology

Please refer to separate Clinical Microbiology review.

4.3 Preclinical Pharmacology/Toxicology

Please refer to separate Nonclinical Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

Please refer to separate Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Listing of Clinical Trials Relevant to DHP Review of BLA 761088

Study	Design	Population	N	Status	Cut-off (BLA)
Trials to Support Safety and Efficacy					
CT-P10 3.3	Phase 1/3 randomized	Advanced Follicular Lymphoma	Enrolled: 140 <u>Part 1</u> Enrolled and randomized: 121 CT-P10: 59 Rituxan: 62 <u>Part 2</u> Enrolled and randomized: 140 (including 121 from Part 1) CT-P10: 70 Rituxan: 70	Ongoing	27 June 2016
(b) (4)					
Additional Trials to Support Safety					
CT-P10 3.4	Phase 3 randomized	Low Tumor Burden Follicular Lymphoma	216 (safety population)	Ongoing	-
Trials to Support Clinical Pharmacology (PK)					
CT-P10 3.2	Phase 3 randomized	Rheumatoid Arthritis	372 (Main Study Period) 295 (Extension Study Period)	Completed	-

5.2 Review Strategy

The key materials used for the review of CT-P10 (TRUXIMA) include:

- BLA datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to information requests from review team
- Major safety analyses were reproduced

5.3 Discussion of Individual Studies/Clinical Trials

Please refer to Section 6 for detailed discussion of Study CT-P10 3.3

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

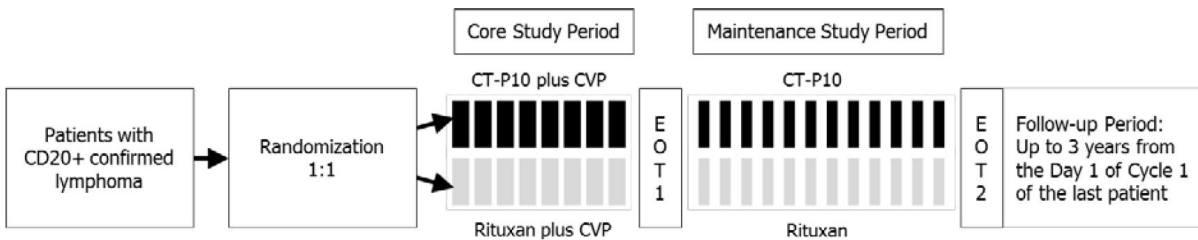
Overview and Objectives

Study CT-P10 3.3 was a Phase 1/3 prospective, randomized, parallel-group, active-controlled, double-blind, multicenter, international study with 2 primary endpoints designed to demonstrate similarity in pharmacokinetics (Part 1), as well as non-inferiority in efficacy (Part 2) of CT-P10 to Rituxan when co-administered with CVP and to assess pharmacodynamics (PD) and safety in patients with advanced (stage III-IV) FL.

Trial Design

As depicted in Figure 1, the study consisted of the following periods: **Screening Period** (up to 4 weeks), **Core Study Period** (up to 8 cycles), **Maintenance Study Period** (up to 2 years) and **Follow-up Period** (until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient).

Figure 1. Study CT-P10 3.3 Schema



Randomization and Stratification

Patients were randomly assigned to treatment groups using a computer-generated randomization schedule prepared before the study. The randomization was balanced by using permuted blocks and was stratified by country, gender, and Follicular Lymphoma International Prognostic Index (FLIPI) score (0 to 2 versus 3 to 5).

It was planned that approximately 134 patients were to be enrolled in this study in total.

- The initial 120 patients were to be enrolled in Part 1 and were to be randomly assigned in a 1:1 ratio to receive CT-P10 (approximately 60 patients) or Rituxan (approximately 60 patients) in combination with CVP. All subsequent patients were to be enrolled in Part 2.
- All patients from Part 1 of the study were to be included in Part 2 of the study and underwent all assessments performed in Part 2.
- In Part 2, approximately 134 patients (including the 120 patients from Part 1) were to be randomly assigned in a 1:1 ratio to CT-P10 (67 patients) or Rituxan (67 patients).

Core Study Period

Patients were screened within the 28 days prior to Day 1 of Cycle 1 of the Core Study Period.

During the Core Study Period, patients were treated with:

- Study drug (CT-P10 or Rituxan) in combination with CVP for up to 8 cycles.
 - On Day 1 of Cycle 1, patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study and were randomly assigned to receive either CT-P10 or Rituxan (375 mg/m² intravenous [IV]).
 - On the first day of each 21-day (±3 days) dosing cycle, patients received an IV infusion of study drug.
 - Premedication consisting of an antipyretic (e.g., paracetamol), an antihistamine (e.g., H1 antihistamine) and a glucocorticoid (prednisone or

prednisolone [40 mg/m² orally]) was administered 30 minutes before each infusion of study drug.

- Patients received cyclophosphamide (750 mg/m² IV) and vincristine (1.4 mg/m² [up to a maximum of 2 mg] IV) after the IV infusion of study drug on the first day of each cycle. Patients received prednisone or prednisolone (40 mg/m² orally on Days 1 through 5) of each 21-day (±3 days) dosing cycle.
- Patients with stable disease and progressive disease during the Core Study Period were discontinued from study treatment and entered into the Follow-up Period. The first end-of-treatment (EOT1) visit occurred 3 weeks (±3 days) after the last dose of study drug in the Core Study Period. During the EOT1 visit, investigators determined whether patients qualified to continue in the Maintenance Study Period.

Table 3. Route of Administration, Dose, and Regimen of Treatment: Core Study Period in Study CT-P10 3.3

Study Treatment	Route of Administration	Dose	Frequency
Prednisone	Oral	40 mg/m ²	Days 1 through 5 of each 21-day cycle (for 8 cycles)
CT-P10 or Rituxan	IV infusion	375 mg/m ²	Day 1 of each 21-day cycle (for 8 cycles)
Cyclophosphamide	IV infusion	750 mg/m ²	
Vincristine	IV infusion	1.4 mg/m ² (maximum 2 mg)	

Maintenance Study Period

- Patients who experienced CR, CRu, or PR after Cycle 8 of the Core Study Period as assessed at the first EOT visit qualified for the Maintenance Study Period.
- If a patient withdrew before the completion of the Core Study Period, the patient was not entered into the Maintenance Study Period.
- The first dose in the Maintenance Study Period was administered after 2 months from the last dose in the Core Study Period (i.e., Day 1 of Cycle 8).

During the Maintenance Study Period, patients were treated with:

- Study drug without CVP once every 2 months (±7 days) from the last dose of study drug for a maximum of 12 cycles (up to 2 years).

- Premedication consisting of an antipyretic (e.g., paracetamol), an antihistamine (e.g., H1 antihistamine), and glucocorticoid during the Maintenance Study Period was administered 30 minutes before each infusion of study drug.
- The second EOT visit occurred 2 months (± 7 days) after the last dose of study drug in the Maintenance Study Period.

Follow-up Period

- Patients who did not qualify for the Maintenance Study Period and patients who completed the Maintenance Study Period entered the Follow-up Period after 3 months from the last visit.
- The Follow-up Period was defined as until death or 3 years from Day 1 of Cycle 1 of the Core Study Period for the last patient.
- During the Follow-up Period, patients were monitored every 3 months for disease status, until treatment with new anticancer therapy or disease progression. Anticancer therapy and survival were to be monitored every 3 months until death or study termination.

Definitions

- Study treatment completion was defined as completing the Core Study Period and the Maintenance Study Period.
- Early discontinuation was defined as not completing the Core Study Period.
- Discontinuation was defined as not completing the Maintenance Study Period.
- Study termination was defined as the date on which the last patient completed the last visit.
- This study was monitored by an independent DSMB comprised of a PK specialist, statistician, chairing physician, and an independent physician.

Inclusion Criteria

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

1. Patient was male or female 18 years or older.
2. Patient had histologically confirmed FL according to the World Health Organization 2008 classification (Jaffe 2009); grades 1 to 3a based on local laboratory review.
3. Patient had at least 1 measurable tumor mass that had not previously been irradiated, and the mass was:
 - a. nodal lesion >15 mm in the longest dimension; or
 - b. nodal lesion >10 mm to ≤ 15 mm in the longest dimension and >10 mm in the shortest dimension; or
 - c. extranodal lesion with both long and short dimensions ≥ 10 mm

4. Patient had confirmed CD20+ lymphoma, as assessed by local laboratory review.
5. Patient had Ann Arbor stage III or IV disease.
6. Patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Oken *et al* 1982).
7. For both male and female patients and their partners of childbearing potential, patient agreed to practice total abstinence or to use one of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study treatment (excluding women who were not of childbearing potential and men who were sterilized):
 - a. Barrier contraceptives (male condom, female condom or diaphragm with a spermicidal gel)
 - b. Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
 - c. Intrauterine devices

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

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

8. For both premenopausal women and women who were 8. less than or equal to 12 months after the onset of menopause, patient had a negative serum pregnancy test during the Screening Period.
9. Patient had adequate bone marrow, hepatic, and renal function reserve as evidenced by:
 - a. Hemoglobin level of ≥ 8 g/dL
 - b. Absolute neutrophil count (ANC) of $\geq 1500/\text{mm}^3$
 - c. Platelet count of $\geq 75000/\text{mm}^3$
 - d. Total bilirubin level of ≤ 2.0 mg/dL
 - e. Aspartate aminotransferase and alanine aminotransferase levels of $\leq 3 \times$ the upper limit of normal (ULN) for the reference laboratory ($\leq 5 \times$ ULN for the reference laboratory with known hepatic involvement by lymphoma)
 - f. A serum creatinine level of $\leq 1.5 \times$ ULN for the reference laboratory, or a calculated creatinine clearance by the Cockcroft-Gault equation (Rostoker *et al* 2007) of ≥ 50 mL/min
10. Patient was able to understand verbal and/or written instructions and to comply with all study requirements.
11. Patient was informed, given ample time and opportunity to read and/or understand about participation in the study, and had signed and dated the written ICF.

Exclusion Criteria

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

1. Patient had received rituximab (or a rituximab proposed biosimilar product), cyclophosphamide, or vincristine.
2. Patient had allergies or hypersensitivity to murine, chimeric, human or humanized proteins, cyclophosphamide, vincristine, or prednisone.
3. Patient had evidence of histological transformation to high-grade or diffuse large B-cell lymphoma.
4. Patient had known central nervous system involvement.
5. Patient had received previous treatment for NHL:
 - a. Previous treatment including chemotherapy, radiotherapy, immunotherapy, and/or surgery (except previous biopsy). However, patients who had received radiotherapy as part of the palliative therapy were eligible if the last fraction of radiotherapy was administered at least 4 weeks prior to Day 1 of Cycle 1 and patients had recovered from all radiotherapy-related toxicities prior to randomization.
 - b. All doses of glucocorticoid therapy for treatment of NHL
 - c. Glucocorticoid therapy during the previous 4 weeks from Day 1 of Cycle 1, with prednisone >20 mg per day for any purpose
6. Patient had current diagnosis of active tuberculosis (TB) (defined by chest x-ray, computed tomography [CT], or proper image) or other severe infections, such as sepsis, abscesses, or opportunistic infections.
7. Patient had a known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. (Carriers of hepatitis B were not permitted to enroll into the study.)
8. Patient had New York Heart Association (Raphael *et al* 2007) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 6 months before Day 1 of Cycle 1.
9. Patient had any malignancy other than NHL, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before Day 1 of Cycle 1.
10. Patient had current or recent (within 30 days before Day 1 of Cycle 1) treatment with any other investigational medicinal product or device.
11. Patient had uncontrolled diabetes mellitus, even after insulin treatment.
12. Patient was pregnant or lactating. Patients who were planning to be pregnant or to breastfeed before, during, or within 12 months after the last infusion of study treatment were not permitted to enroll into the study.
13. Patient was taking a live, live-attenuated, or nonlive vaccine within 4 weeks before Day 1 of Cycle 1 of study treatment.
14. Patient had evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that

contraindicated the use of an investigational product, or patient was a high risk for treatment complications.

Study Endpoints

This study comprised 2 parts: (1) for Part 1, pharmacokinetics was the primary endpoint, and (2) efficacy was the primary endpoint for Part 2.

The primary PK endpoints that were evaluated were AUC_{τ} and $C_{\max SS}$ at Core Cycle 4.

The primary efficacy endpoint for Part 2 was ORR (the proportion of responders who achieved CR, CRu or PR) during the Core Study Period, according to the 1999 IWG criteria.

Statistical Analysis Plan

Please refer to separated Biometrics review for detailed discussion of the SAP.

Protocol Amendments

A total of 11 minor country-specific and global protocol amendments are listed in the CSR. Most notable were global protocol amendments related to study eligibility criteria and statistical considerations in the amendment dated 24 July 2014.

6.1.2 Demographics

Table 4. Demographic Characteristics: ITT Population (Part 1)

	CT-P10 (N=59) n (%)	Rituxan (N=62) n (%)	Total (N=121) n (%)
Age (years)			
Mean (SD)	54.7 (14.3)	56.8 (14.3)	55.8 (14.3)
Median (min, max)	54.0 (30, 85)	58.5 (26, 84)	56.0 (26, 85)
Gender			
Female	33 (55.9)	32 (51.6)	65 (53.7)
Male	26 (44.1)	30 (48.4)	56 (46.3)
Race			
White or Caucasian	42 (71.2)	49 (79.0)	91 (75.2)
Asian	11 (18.6)	10 (16.1)	21 (17.4)
Hispanic or Latino	5 (8.5)	1 (1.6)	6 (5.0)
Black or African American	1 (1.7)	0	1 (0.8)
Other	0	1 (1.6)	1 (0.8)
Not allowed by investigator country regulation	0	1 (1.6)	1 (0.8)
Region			
European Union	23 (39.0)	30 (48.4)	53 (43.8)
Non-European Union	36 (61.0)	32 (51.6)	68 (56.2)
ECOG Performance Status at Screening			
0	37 (62.7)	42 (67.7)	79 (65.3)
1	21 (35.6)	19 (30.6)	40 (33.1)
2	1 (1.7)	1 (1.6)	2 (1.7)
3-5	0	0	0

Source: CSR Table 11-3

Table 5. Demographic Characteristics: ITT Population (Part 2)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Age (years)			
Mean (SD)	55.0 (13.7)	56.5 (14.1)	55.8 (13.9)
Median (min, max)	57.0 (30, 85)	58.5 (26, 84)	57.5 (26, 85)
Gender			
Female	40 (57.1)	37 (52.9)	77 (55.0)
Male	30 (42.9)	33 (47.1)	63 (45.0)
Race			
White or Caucasian	51 (72.9)	52 (74.3)	103 (73.6)
Asian	11 (15.7)	13 (18.6)	24 (17.1)
Hispanic or Latino	6 (8.6)	3 (4.3)	9 (6.4)
Black or African American	2 (2.9)	0	2 (1.4)
Other	0	1 (1.4)	1 (0.7)
Not allowed by investigator country regulation	0	1 (1.4)	1 (0.7)
Region			
European Union	28 (40.0)	32 (45.7)	60 (42.9)
Non-European Union	42 (60.0)	38 (54.3)	80 (57.1)
ECOG Performance Status at Screening			
0	44 (62.9)	47 (67.1)	91 (65.0)
1	25 (35.7)	22 (31.4)	47 (33.6)
2	1 (1.4)	1 (1.4)	2 (1.4)
3-5	0	0	0

Source: CSR Table 11-4

Reviewer Comment: Demographic characteristics were largely balanced between both study groups.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

APPEARS THIS WAY ON ORIGINAL

Table 6. Summary of Pathological Diagnosis (Screening): ITT Population (Part 2)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Lymphoma disease duration (months)¹			
Mean (SD)	3.4 (7.3)	2.4 (2.9)	2.9 (5.6)
Median (min, max)	1.7 (0.3, 57.1)	1.6 (0.3, 20.1)	1.6 (0.3, 57.1)
Follicular CD20+ Lymphoma Diagnosis			
Yes	70 (100)	70 (100)	140 (100)
Follicular Lymphoma Grade at Initial Diagnosis			
Grade 1 ²	23 (32.9)	21 (30.0)	44 (31.4)
Grade 2	34 (48.6)	32 (45.7)	66 (47.1)
Grade 3a	12 (17.1)	16 (22.9)	28 (20.0)
Grade 3b	0	0	0
Unknown ^{3,4}	1 (1.4)	1 (1.4)	2 (1.4)
Follicular Lymphoma Grade at Screening			
Grade 1 ²	21 (30.0)	20 (28.6)	41 (29.3)
Grade 2	36 (51.4)	34 (48.6)	70 (50.0)
Grade 3a	12 (17.1)	16 (22.9)	28 (20.0)
Grade 3b	0	0	0
Unknown ⁴	1 (1.4)	0	1 (0.7)

Source: CSR Table 11-5

1. Disease duration of lymphoma was calculated as duration = (date of first infusion – date of first diagnosis)
2. For Patient (b) (6) in the CT-P10 treatment group, pathologic diagnosis was Grade 1 FL at screening based on bone marrow, flow cytometry report and other available blood tests. However, grade could not be assured as lymph node biopsy had not been performed. This patient was excluded from the per-protocol population due to this major protocol violation.
3. For Patient (b) (6) in the Rituxan treatment group, pathologic diagnosis was Grade 3 FL at initial diagnosis but was not identified as a or b. This patient was eligible at screening with FL grade 2.
4. Patient (b) (6) in the CT-P10 treatment group did not have a source document to identify FL grade, but FL was diagnosed with bone marrow specimen. This patient was excluded from the per-protocol population due to this major protocol violation.

Table 7. Ann Arbor Staging and FLIPI Score: ITT Population (Part 2)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Ann Arbor Staging at Screening			
Stage I	0	0	0
Stage II	0	0	0
Stage III	21 (30.0)	36 (51.4)	57 (40.7)
Stage IV	49 (70.0)	34 (48.6)	83 (59.3)
FLIPI at Screening			
0	0	0	0
1	8 (11.4)	6 (8.6)	14 (10.0)
2	25 (35.7)	21 (30.0)	46 (32.9)
3	23 (32.9)	30 (42.9)	53 (37.9)
4	10 (14.3)	12 (17.1)	22 (15.7)
5	4 (5.7)	1 (1.4)	5 (3.6)

Source: CSR Table 11-6

Reviewer Comment: Baseline characteristics, including pathologic diagnosis and staging, were largely balanced between both groups and thus unlikely to lead to clinically meaningful differences between treatment arms.

6.1.3 Subject Disposition

Table 8. Patient Disposition: ITT Population (Part 1)

	CT-P10 (N=59) n (%)	Rituxan (N=62) n (%)	Total (N=121) n (%)
Total number of patients in Part 1			
Screened ¹			159
Primary reason for screening failure ²			
Inclusion/exclusion criteria not met			30
Patient withdrew consent			3
Other			5
Randomized	59 (100)	62 (100)	121 (100)
Initiated core study treatment³	59 (100)	62 (100)	121 (100)
Completed up to and including Core Cycle 4	55 (93.2)	58 (93.5)	113 (93.4)
Early discontinued before completion of Core Cycle 4	4 (6.8)	4 (6.5)	8 (6.6)
Completed Core Study Period	52 (88.1)	56 (90.3)	108 (89.3)

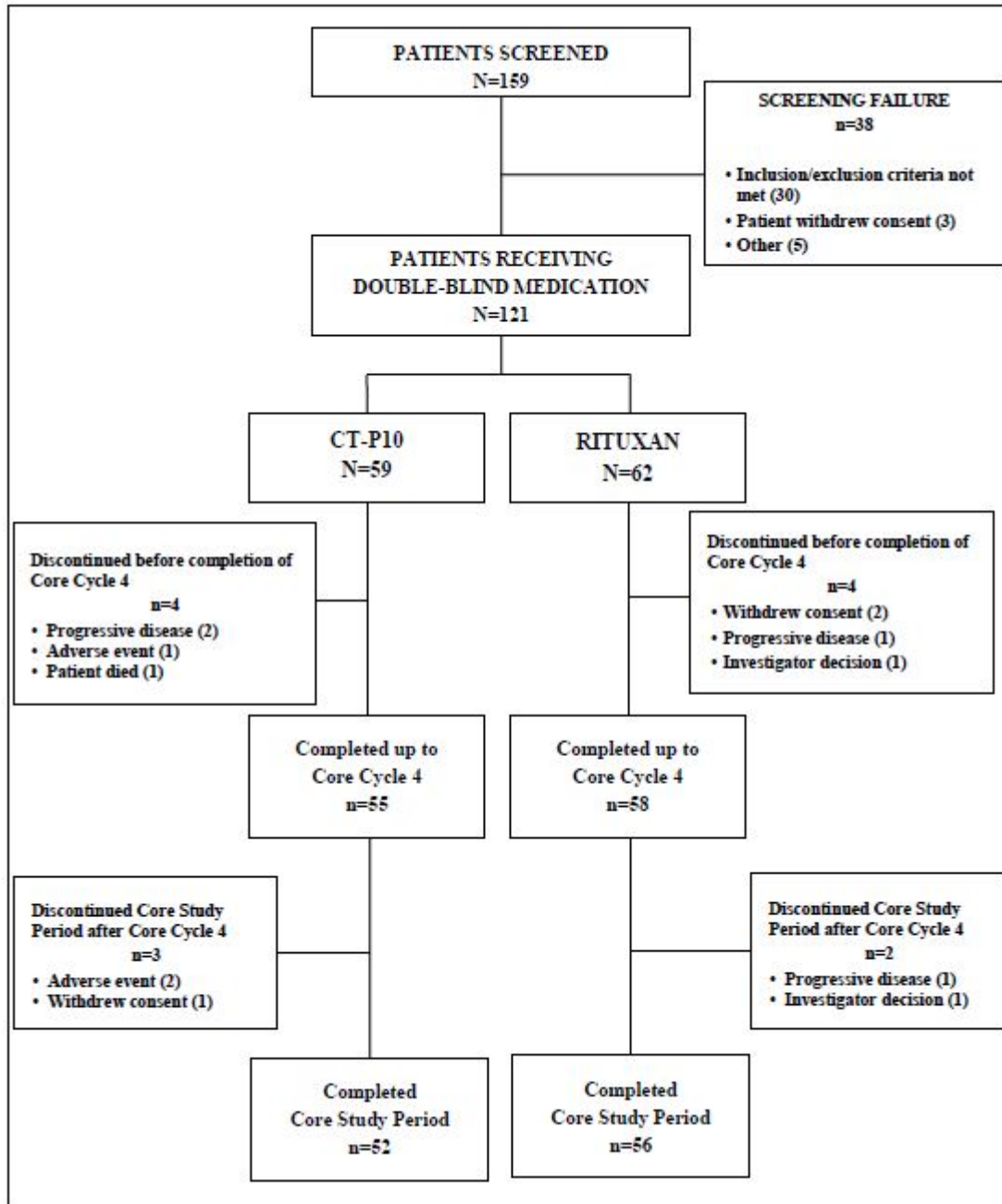
Early discontinued before completion of the Core Study Period ⁴	7 (11.9)	6 (9.7)	13 (10.7)
Primary reason for early discontinuation during the Core Study Period			
Progressive Disease ⁵	2 (3.4)	2 (3.2)	4 (3.3)
Adverse Event ⁶	3 (5.1)	0	3 (2.5)
Patient died (tumor lysis syndrome) ⁷	1 (1.7)	0	1 (0.8)
Withdrew consent	1 (1.7)	2 (3.2)	3 (2.5)
Investigator decision ⁸	0	2 (3.2)	2 (1.7)

Source: CSR Table 10-1

Note: Unless otherwise stated, percentages were calculated using the intent-to-treat population as the denominator.

1. Included screening failures and randomly assigned patients. Patients who were screened and randomly assigned were displayed in the “Randomized” row.
2. This summary included screening failures and nonrandomized patients only.
3. Included patients who were randomly assigned and initiated treatment.
4. Included all patients who were early discontinued during the Core Study Period.
5. Last administered dose was at Core Cycle 2 for Patient (b) (6) and at Core Cycle 4 for Patient (b) (6) in the CT-P10 treatment group and at Core Cycle 2 for Patient (b) (6) and at Core Cycle 7 for Patient (b) (6) in the Rituxan treatment group.
6. Patient (b) (6) (angina pectoris), Patient (b) (6) (infusion-related reaction) and Patient (b) (6) (liver function test abnormal) discontinued after the infusion at Core Cycle 3, 4 and 6, respectively.
7. Patient (b) (6) died due to tumour lysis syndrome after the infusion at Core Cycle 1.

Figure 2. Patient Disposition (Part 1)



Source: CSR Figure 10-1

Table 9. Patient Disposition: ITT Population (Part 2)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Total number of patients in Part 2			
Screened ¹			184
Primary reason for screening failure ²			
Inclusion/exclusion criteria not met			35
Patient withdrew consent			3
Other			6
Randomized	70 (100)	70 (100)	140 (100)
Initiated core study treatment³	70 (100)	70 (100)	140 (100)
Completed Core Study Period	62 (88.6)	62 (88.6)	124 (88.6)
Early discontinued before completion of the Core Study Period	8 (11.4)	8 (11.4)	16 (11.4)
Primary reason for early discontinuation during the Core Study Period			
Progressive Disease ⁴	2 (2.9)	3 (4.3)	5 (3.6)
Adverse Event ⁵	4 (5.7)	1 (1.4)	5 (3.6)
Patient died (tumor lysis syndrome) ⁶	1 (1.4)	0	1 (0.7)
Withdrew consent	1 (1.4)	2 (2.9)	3 (2.1)
Investigator decision ⁷	0	2 (2.9)	2 (1.4)
Number of deaths	3 (4.3)	0	3 (2.1)
Reason for death			
Lymphoma ⁸	2 (2.9)	0	2 (1.4)
Adverse event (tumor lysis syndrome) ⁶	1 (1.4)	0	1 (0.7)

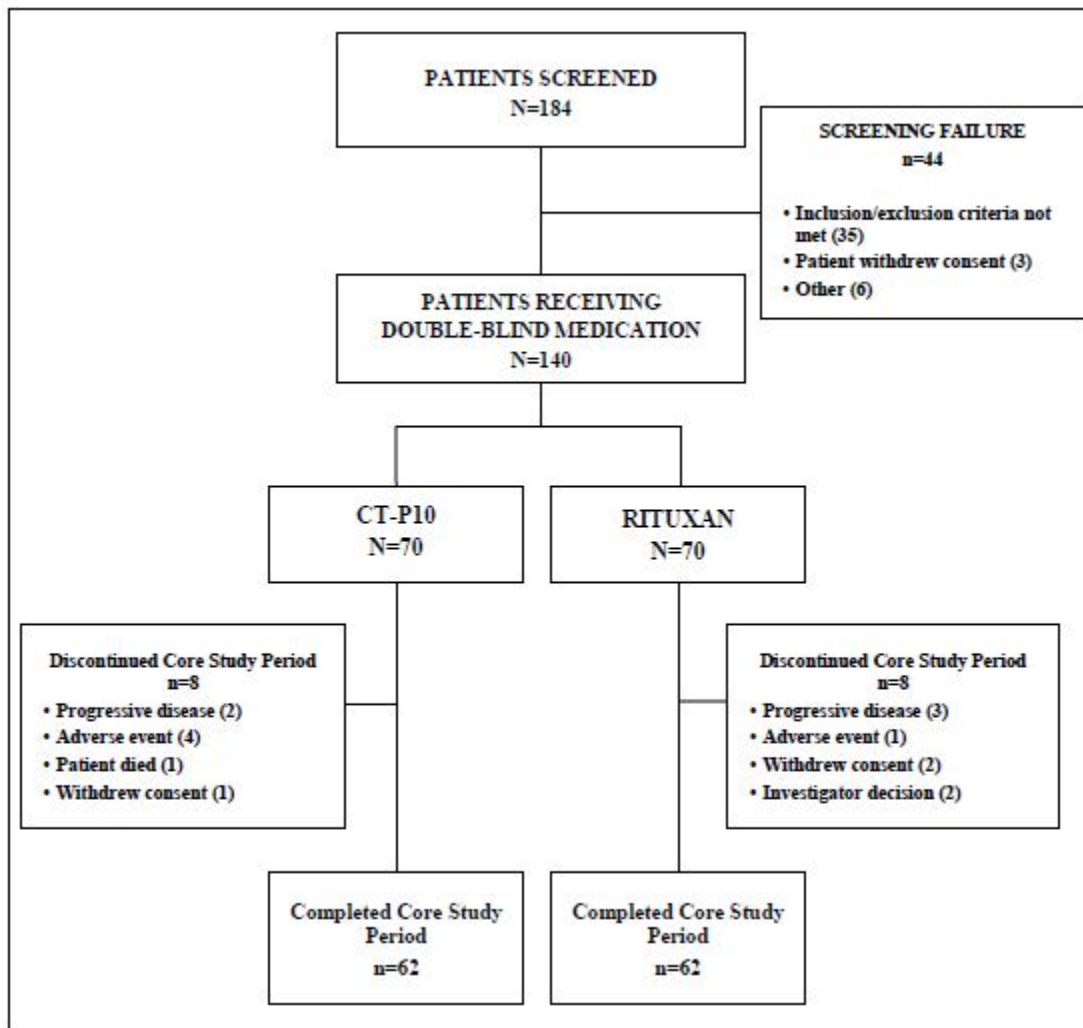
Source: CSR Table 10-2

Note: Unless otherwise stated, percentages were calculated using the intent-to-treat population as the denominator.

1. Includes screening failures and randomly assigned patients. If a patient was screened and randomly assigned, the treatment assigned was displayed in the “Randomized” row.
2. This summary includes screening failures and nonrandomized patients only.
3. Includes patients who were randomly assigned and initiated treatment.
4. Last administered dose was Core Cycle 2 for Patient (b) (6) and Core Cycle 4 for Patient (b) (6) in the CT-P10 treatment group and Core Cycle 2 for Patient (b) (6) Core Cycle 4 for Patient 3 (b) (6) and Core Cycle 7 for Patient (b) (6) in the Rituxan treatment group.

5. Patient (b) (6) (angina pectoris) discontinued study treatment after the infusion at Core Cycle 3, Patient (b) (6) (infusion-related reaction) after the infusion at Core Cycle 4, Patient (b) (6) (liver function test abnormal) after the infusion at Core Cycle 6, Patient (b) (6) (post procedural fistula) after the infusion at Core Cycle 3 in the CT-P10 treatment group. Patient (b) (6) (tuberculosis) after the infusion at Core Cycle 5 in the Rituxan treatment group.
6. Patient (b) (6) died due to tumor lysis syndrome after the infusion at Core Cycle 1.
7. Patient (b) (6) discontinued study treatment as the investigator considered not sufficient response to the study drug was assessed after the infusion at Core Cycle 2 and Patient (b) (6) had a response of stable disease and discontinued study treatment as the investigator followed their routine practice after the infusion at Core Cycle 6.
8. Patient (b) (6) died due to progressive disease during the Follow-up period after 184 days from the last study drug administration. This patient had discontinued study treatment due to progressive disease after the infusions at 2 cycles of CT-P10 in the Core Study Period. Patient (b) (6) died due to progressive disease during the Follow-up period after 351 days from the last study drug administration. This patient had discontinued study treatment due to infusion-related reaction after the infusions of CT-P10 for 4 cycles in the Core Study Period.

Figure 3. Patient Disposition (Part 2)



Source: CSR Figure 10-2

Protocol Violations/Deviations

Three major protocol deviations reported were noncompliance with inclusion/exclusion criteria (3 [4.3%] patients in the CT-P10 treatment group). For the 2 patients (Patients (b) (6)), pathologic diagnosis was performed using bone marrow tissue only, and therefore, inclusion criterion #2 (histologically confirmed grade 1-3 FL based on local laboratory review) was not confirmed. Therefore, the possibility of high grade of lymphoma could not be ruled out. One patient (Patient (b) (6)) violated the exclusion criterion #5 (previous treatment for non-Hodgkin's lymphoma) since the patient underwent a previous surgery including removal of intra-abdominal lesion related to FL and small bowel resection.

Three patients were excluded from per-protocol population as efficacy assessment was not performed after treatment. Patient (b) (6) was early discontinued after the infusion at Core Study Period cycle 1 because the patient died due to tumour lysis syndrome in the CT-P10 treatment group.

These protocol deviations are summarized in Table 10 below.

Table 10. Major Protocol Deviations and Other Reasons for Exclusion: ITT Population (Part 2)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)	Excluded Populations
Major protocol deviations				
Noncompliance with eligibility criteria	3 (4.3)	0	3 (2.1)	Per-protocol
Other reasons for exclusion				
No response evaluation after treatment	1 (1.4)	2 (2.9)	3 (2.1)	Per-protocol

Source: CSR Table 10-3

Reviewer Comment: The small number of protocol deviations was unlikely to impact the conclusions of the analyses.

6.1.4 Analysis of Primary Endpoint(s)

Please refer to separate Biometrics review of efficacy.

6.1.5 Analysis of Secondary Endpoints(s)

Please refer to separate Biometrics review of efficacy.

6.1.6 Other Endpoints

Please refer to separate Biometrics review of efficacy.

6.1.7 Subpopulations

Please refer to separate Biometrics review of efficacy.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Please refer to separate Biometrics review of efficacy.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety Summary

The clinical safety data supporting this BLA is primarily derived from the Phase 1/3 randomized, parallel-group, active-controlled, double-blind study to demonstrate equivalence of PK and noninferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with CVP in patients with advanced follicular lymphoma. There were n=70 patients in each arm of the study (N=140).

Key safety findings from Study CT-P10 3.3, and from the supportive safety database:

- **Deaths:** There was 1 death (1 in the CT-P10 group and 0 in the Rituxan group) within 30 days of study treatment attributable to tumour lysis syndrome.

- **Serious Adverse Events (SAEs) and Discontinuations:** Overall, TASAEs were more common in CT-P10 group. These were more frequent in the CT-P10 group across a number of SOCs; there did not appear to be a clinically meaningful clustering of events. Compared with Rituxan (12.9%), 22.9% patients experienced at least one TESA. There were more patients with at least one TEAE leading to permanent study drug discontinuation in the CT-P10 group vs. Rituxan group (7.1% vs. 1.4%).
- **Grade 3 and 4 Adverse Reactions:** At the preferred term level, Grade 3 or higher TEAEs were more frequent in the CT-P10 group. Twenty-six (37.1%) and 20 (28.6%) patients experienced one or more Grade 3 or higher TEAE in the CT-P10 and Rituxan arms, respectively. Notably, Grade 3 or higher neutropenia was more frequent in the CT-P10 group (25.7% vs. 15.7% Rituxan group) as was pneumonia (5.7% vs 0% in the Rituxan group).
- **Common Adverse Reactions:** In Study CT-P10 3.3, the common preferred-term level TEAEs (i.e., $\geq 3\%$ of patients) in the CT-P10 arm were Neutropenia (34.3%), infusion related reaction (22.9%), constipation (17.1%), neuropathy peripheral (14.3%), and alopecia (14.3%). The most frequently reported TEAEs in the Rituxan arm were infusion related reaction (24.3%), neutropenia (22.9%), upper respiratory tract infection (17.1%), and neuropathy peripheral (17.1%).

7.1.2 Categorization of Adverse Events

The clinical safety data supporting this BLA is primarily derived from the Phase 1/3 randomized, parallel-group, active-controlled, double-blind study to demonstrate equivalence of PK and noninferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with CVP in patients with advanced follicular lymphoma. There were n=70 patients in each arm of the study (N=140). The Applicant also submitted supportive unblinded safety data for CT-P10 from Study CT-P10 3.4 X2106.

The key data reviewed for clinical safety includes:

- Clinical study report for Study CT-P10 3.3
- Summary of Clinical Safety
- Raw and derived datasets for Study CT-P10 3.3
- Narratives for Study CT-P10 3.3
- Case report forms for Study CT-P10 3.3

AEs reported throughout the study were coded to a preferred term and body system using MedDRA 18.1. Adverse events were graded for severity according to CTCAE Version 4.0.

Listings for AEs occurring during the study were provided by treatment group. The data listing included the following information from the eCRF: SOC, verbatim reported term and PT; start and stop date; frequency (intermittent, continuous); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); any treatment required (no, yes with specified treatment); severity (CTCAE grade 1-5); action taken by investigator to study drug and CVP (no action taken, dose decreased, dose interruption (or prolonged), permanently discontinued, dose delay); relationship to study drug and CVP (unrelated, possible, probable, definite); and whether the event was serious (no, yes).

Summaries of AEs were presented overall and by study period (Core, Maintenance, and Follow-up). Any AE reported in the eCRF having a start date on or after the Core Cycle 1 visit date and before the Maintenance Cycle 1 visit date or Follow-up 1 visit date (in cases where maintenance cycle visits were not populated) was included in the Core Study Period. Any AE reported in the eCRF having a start date on or after the Maintenance Cycle 1 visit date and before the Follow up 1 visit date was included in the Maintenance Study Period.

Treatment-emergent AEs during the study were summarized overall and by study period (Core, Maintenance, and Follow-up), by relationship to study drug, severity, SOC, and PT for the safety population, displaying the number and percentage of patients with at least 1 TEAE using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least 1 TEAE over all SOCs were also displayed.

An SAE was defined as any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Important medical events that did not result in death, were not life threatening, or did not require hospitalization were able to be considered an SAE when, based upon appropriate medical judgment, they jeopardized the patient and could have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment-emergent SAEs (TESAEs) were summarized overall and by study period (Core, Maintenance, and Follow-up), by relationship to study drug, severity/serious criteria, SOC and PT displaying the number and percentage of patients with at least 1 TESAE using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least 1 TESAE over all SOCs were also displayed.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. The clinical safety data supporting this BLA is primarily derived from the Phase 1/3 Study CT-P10 3.3 which comprised 140 subjects (70 patients in each the CT-P10 and Rituxan arms).

Reviewer Comment: *The randomized, double-blinded Study CT-P10 3.3 is of adequate size to serve as the safety database considering exposure to the appropriate doses, duration of treatment, patient demographics, and disease characteristics with reference to the U.S. target population.*

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During the Core Study Period (up to Core Cycle 8), the mean (SD) of relative dose intensity was similar between the 2 treatment groups; 97.7% (4.40%) and 98.3% (2.71%) in the CT-P10 and Rituxan group, respectively. Similarly, the median relative dose intensity during this time was 99.3% and 99.0%.

The total number of patients whom received each dose during the Core Study Period (up to Core Cycle 8) is presented in Table 11.

Table 11. Overall Exposure to CT-P10 or Rituxan up to Core Cycle 8 in Study CT-P10 3.3 (Part 2): Safety Population

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Core Cycle 1 at Week 0	70 (100.0)	70 (100.0)	140 (100.0)
Core Cycle 2 at Week 3	69 (98.6)	68 (97.1)	137 (97.9)
Core Cycle 3 at Week 6	68 (97.1)	66 (94.3)	134 (95.7)
Core Cycle 4 at Week 9	66 (94.3)	66 (94.3)	132 (94.3)
Core Cycle 5 at Week 12	64 (91.4)	65 (92.9)	129 (92.1)
Core Cycle 6 at Week 15	63 (90.0)	64 (91.4)	127 (90.7)
Core Cycle 7 at Week 18	62 (88.6)	63 (90.0)	125 (89.3)

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Core Cycle 8 at Week 21	62 (88.6)	62 (88.6)	124 (88.6)

Source: CSR Table 14.1.14, Summary of Clinical Safety Table 2.7.4-4

Reviewer comment: Study drug dose intensity and overall exposure appear to be similar in each study arm.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Blood samples (including samples for beta-2 microglobulin) and urine samples for clinical laboratory assessments were collected at the time points specified in the Study CT-P10 3.3 protocol. Blood samples were not collected in a fasting state unless, in the opinion of the investigator, fasting blood samples were required.

A serum pregnancy test (local laboratory) was conducted at screening and at both the EOT visits, and then a urine pregnancy test for women of childbearing potential who had not been surgically sterilized was used to confirm that patients were not pregnant before dosing on Day 1 of each cycle in the Core Study Period and Maintenance Study Period.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to separate Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse events for similar drugs in drug class has been reviewed in Section 2.4 Important Safety Issues with Consideration to Related Drugs.

7.3 Major Safety Results

7.3.1 Deaths

Table 12. CT-P10 3.3 Summary of Deaths (All Treated Population)

Primary Cause of Death	CT-P10 plus CVP (N=70) n (%)	Rituxan plus CVP (N=70) n (%)
Patients who Died		
Disease Progression	2	0
Other	1	0
Within 30 Days of Last Dose		
Disease Progression	0	0
Other	1	0
After 30 days of Last Dose		
Disease Progression	2	0
Other	0	0

Reviewer comment: In the 4-month safety update (cut-off date 31 January 2017), a total of 6 deaths, which include 3 deaths due to adverse event (2 deaths in the CT-P10 group and 1 death in the Rituxan group) and 3 deaths attributed to disease progression (2 deaths in the CT-P10 group and 1 death in the Rituxan group), were observed in Study CT-P10 3.3. The 3 additional deaths since the original submission are listed below:

CT-P10 Group:

Subject (b) (6) – Gastric adenocarcinoma (2nd primary cancer)

Rituxan Group:

Subject (b) (6) – Respiratory tract infection

Subject (b) (6) – Disease progression

Summary of Deaths (Other Causes) within 30 Days of Last Dose (CT-P10 group)

Table 13 below summarizes the narratives for the patients in the CT-P10 group with reasons for death other than disease progression within 30 days of the last CT-P10 dose.

Table 13. CT-P10 3.3 Deaths for Other than Disease Progression Up to 30 Days of Last Dose (All Treated Population)

Patient ID Group	Summary of Case	Reviewer Comment
(b) (6) CT-P10	74 year old female who was treated with 1 cycle of CT-P10 plus CVP on (b) (6). (b) (6) experienced TEAE reported as tumor lysis syndrome on (b) (6) and died due to cardiac and renal failure on 09 (b) (6) (Day 16). The patient had a history of coronary artery disease, cerebral atherosclerosis and hypertension prior to study enrollment. The causes of death was reported as cardiac and renal failure. An autopsy was not performed. The event of tumour lysis syndrome was considered by the investigator to be possibly related to CT-P10 and cyclophosphamide, and unrelated to vincristine and prednisolone.	This death is possibly attributable to CT-P10.

Summary of Deaths (All causes) after 30 Days of Last Dose (CT-P10 group)

Two patients in the CT-P10 group died due to disease progression. The CRFs and narratives for these patients were reviewed in detail:

Subject (b) (6) was a 41 year old female who received 2 cycles of CT-P10 plus CVP on (b) (6) and (b) (6) who was subsequently discontinued from the study on (b) (6) due to disease progression and declining health. After study discontinuation, the patient received a total of 4 cycles of rituximab treatment in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone starting on (b) (6) until her death on (b) (6) due to disease progression, 166 days following protocol discontinuation.

Subject (b) (6) was a 61 year old female who received 4 cycles of CT-P10 plus CVP from (b) (6) until (b) (6), but was discontinued from the study due to multiple infusion related reactions. After the study drug CT-P10 discontinuation, the patient received an additional 4 cycles of CVP only and entered the Follow-up Period. During the Follow-up Period, the patient was treated with R-CVP and Ibrutinib in combination with CHOP as a salvage treatment and died due to lymphoma on (b) (6), 351 days from the last study drug administration.

7.3.2 Nonfatal Serious Adverse Events

Overall, TESAEs were more frequent in the CT-P10 group across a number of SOCs; there does not appear to be a clinically meaningful clustering of events. These TESAEs are summarized by SOC and PT in Table 14.

Table 14. Summary of TESAEs in Study CT-P10 3.3 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Total number of TESAEs	29	11	40
Number (%) of patients with ≥1 TESA	16 (22.9)	9 (12.9)	25 (17.9)
Blood and lymphatic system disorders	4 (5.7)	3 (4.3)	7 (5.0)
Anaemia	1 (1.4)	0	1 (0.7)
Febrile neutropenia	2 (2.9)	2 (2.9)	4 (2.9)
Leukopenia	0	1 (1.4)	1 (0.7)
Neutropenia	2 (2.9)	0	2 (1.4)
Pancytopenia	1 (1.4)	0	1 (0.7)
Cardiac disorders	1 (1.4)	0	1 (0.7)
Angina pectoris	1 (1.4)	0	1 (0.7)
Atrial fibrillation	1 (1.4)	0	1 (0.7)
Gastrointestinal disorders	2 (2.9)	2 (2.9)	4 (2.9)
Constipation	1 (1.4)	0	1 (0.7)
Diarrhoea	0	1 (1.4)	1 (0.7)
Ileus	0	1 (1.4)	1 (0.7)
Small intestinal perforation	1 (1.4)	0	1 (0.7)
General disorders and administration site conditions	0	1 (1.4)	1 (0.7)
Pyrexia	0	1 (1.4)	1 (0.7)
Hepatobiliary disorders	1 (1.4)	0	1 (0.7)
Cholecystitis	1 (1.4)	0	1 (0.7)
Immune system disorders	1 (1.4)	0	1 (0.7)
Anaphylactic shock	1 (1.4)	0	1 (0.7)
Infections and infestations	5 (7.1)	2 (2.9)	7 (5.0)
Abdominal infection	1 (1.4)	0	1 (0.7)
Campylobacter gastroenteritis	1 (1.4)	0	1 (0.7)
Encephalitis	0	1 (1.4)	1 (0.7)
Lower respiratory tract infection	1 (1.4)	1 (1.4)	2 (1.4)
Pneumonia	3 (4.3)	0	3 (2.1)
Injury, poisoning and procedural complications	1 (1.4)	1 (1.4)	2 (1.4)
Post procedural fistula	1 (1.4)	0	1 (0.7)
Subdural hematoma	0	1 (1.4)	1 (0.7)
Investigations	1 (1.4)	0	1 (0.7)
Liver function test abnormal	1 (1.4)	0	1 (0.7)
Metabolism and nutrition disorders	2 (2.9)	0	2 (1.4)

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Hypoalbuminaemia	1 (1.4)	0	1 (0.7)
Hypocalcaemia	1 (1.4)	0	1 (0.7)
Hypomagnesaemia	1 (1.4)	0	1 (0.7)
Tumour lysis syndrome	1 (1.4)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	3 (4.3)	1 (1.4)	4 (2.9)
Chronic obstructive pulmonary disease	2 (2.9)	1 (1.4)	3 (2.1)
Pleural effusion	1 (1.4)	0	1 (0.7)
Pulmonary embolism	1 (1.4)	0	1 (0.7)
Vascular disorders	1 (1.4)	1 (1.4)	2 (1.4)
Deep vein thrombosis	1 (1.4)	0	1 (0.7)
Thrombophlebitis	0	1 (1.4)	1 (0.7)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED, CT-P10 3.3 CSR Post-text
 Table 14.3.1.2. Some Preferred Terms (PTs) were combined. See Appendix Section
 Summary of Clinical Safety 2.7.4.7.1 for further details
 TESA: Treatment emergent serious adverse event

Overall, Grade 3 or higher TESAEs were noted only in the CT-P10 group. Notably, there were 3 cases of Grade 3 or higher pneumonia in the CT-P10 group. This is summarized by SOC and PT in Table 15.

Table 15. Summary of $\geq$ Grade 3 TESAEs ($\geq 3\%$ of Patients by PT in Either Treatment Group) in CT-P10 3.3 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Number (%) of patients with ≥ 1 $\geq$Grade 3 TEAEs	3 (4.3)	0	3 (2.1)
Infections and infestations			
Pneumonia	3 (4.3)	0	3 (2.1)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED, Some Preferred Terms (PTs) were combined. See Appendix Section Summary of Clinical Safety 2.7.4.7.1 for further details.

7.3.3 Dropouts and/or Discontinuations

There were more patients with at least one TEAE leading to permanent study drug discontinuation in the CT-P10 group vs. Rituxan group (7.1% vs. 1.4%). These events represented a spectrum of SOCs. These events are summarized in Table 16.

Table 16. TEAEs Leading To Permanent Study Drug Discontinuation in Study CT-P10 3.3 (Part 2), By Intensity: Safety Population

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)
Number of Patients With At Least One TEAEs Leading To Permanent Study Drug Discontinuation	5 (7.1)	1 (1.4)
Total Number of TEAEs Leading To Permanent Study Drug Discontinuation	5	1
Angina pectoris (Grade 3)	1	-
Tuberculosis (Grade 2)	-	1
Infusion related reaction (Grade 2)	1	-
Post procedural fistula (Grade 2)	1	-
Liver function test abnormal (Grade 3)	1	-
Tumour lysis syndrome (Grade 5)	1	-

Sources: CSR Table 14.3.1.4

Reviewer comment: There did not appear to be a clinically significant pattern among the observed TEAEs leading to permanent study drug discontinuation.

7.3.4 Significant Adverse Events

Table 17. Summary of Infusion-Related Reactions (IRRs) in Study CT-P10 3.3: Safety Population

	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)
Number of Events	22	21
Number (%) of patients with ≥ 1 IRR	16 (22.9)	17 (24.3)
Related	15 (21.4)	17 (24.3)
Grade 1 (mild)	4 (5.7)	6 (8.6)
Grade 2 (moderate)	9 (12.9)	11 (15.7)
Grade 3 (severe)	2 (2.9)	0
Unrelated	1 (1.4)	1 (1.4)
Grade 1 (mild)	0	0
Grade 2 (moderate)	1 (1.4)	1 (1.4)
Number (%) of patients with ≥ 1 serious IRR	1 (1.4)	0
Number (%) of patients with ≥ 1 IRR leading to the discontinuation	1 (1.4)	0
Number (%) of patients with ≥ 1 IRR required any treatment	13 (18.6)	16 (22.9)

Sources: CSR Table 14.3.1.5, Listing 14.3.2.5
 IRR: Infusion related reaction

Reviewer comment: There did not appear to be a clinically significant difference in IRRs between the study arms.

7.3.5 Submission Specific Primary Safety Concerns

See Sections 7.3.2, 7.3.3, and 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, TEAEs were comparable in both the CT-P10 and Rituxan groups. Fifty-eight (82.9%) and 56 (80.0%) patients experienced one or more TEAE in the CT-P10 and Rituxan arms, respectively. Notably, neutropenia was more frequent in the CT-P10 group (34.3% vs. 22.9% Rituxan group). These TEAEs are summarized by SOC and PT in Table 18.

Table 18. Summary of TEAEs (≥3% of Patients by PT in Either Treatment Group) in CT-P10 3.3 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Number (%) of patients with ≥ 1 TEAE	58 (82.9)	56 (80.0)	114 (81.4)
Blood and lymphatic system disorders	28 (40.0)	22 (31.4)	50 (35.7)
Anaemia	5 (7.1)	4 (5.7)	9 (6.4)
Neutropenia	24 (34.3)	16 (22.9)	40 (28.6)
Gastrointestinal disorders	27 (38.6)	27 (38.6)	54 (38.6)
Abdominal pain	6 (8.6)	10 (14.3)	16 (11.4)
Constipation	12 (17.1)	9 (12.9)	21 (15.0)
Diarrhoea	4 (5.7)	5 (7.1)	9 (6.4)
Nausea	7 (10.0)	5 (7.1)	12 (8.6)
Stomatitis	1 (1.4)	4 (5.7)	5 (3.6)
Vomiting	3 (4.3)	0	3 (2.1)
General disorders and administration site conditions	12 (17.1)	18 (25.7)	30 (21.4)
Asthenia	3 (4.3)	6 (8.6)	9 (6.4)
Fatigue	4 (5.7)	6 (8.6)	10 (7.1)
Oedema	3 (4.3)	2 (2.9)	5 (3.6)
Pyrexia	2 (2.9)	6 (8.6)	8 (5.7)
Infections and infestations	22 (31.4)	26 (37.1)	48 (34.3)
Lower respiratory tract infection	5 (7.1)	1 (1.4)	6 (4.3)
Pneumonia	5 (7.1)	1 (1.4)	6 (4.3)
Sinusitis	3 (4.3)	1 (1.4)	4 (2.9)
Upper respiratory tract infection	5 (7.1)	12 (17.1)	17 (12.1)
Urinary tract infection	4 (5.7)	4 (5.7)	8 (5.7)
Injury, poisoning and procedural complications	17 (24.3)	18 (25.7)	35 (25.0)
Infusion related reaction	16 (22.9)	17 (24.3)	33 (23.6)
Investigations	7 (10.0)	6 (8.6)	13 (9.3)
Weight decreased	1 (1.4)	3 (4.3)	4 (2.9)
Metabolism and nutrition disorders	6 (8.6)	13 (18.6)	19 (13.6)

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Decreased appetite	0	6 (8.6)	6 (4.3)
Hyperglycaemia	0	5 (7.1)	5 (3.6)
Musculoskeletal and connective tissue disorders	17 (24.3)	16 (22.9)	33 (23.6)
Arthralgia	4 (5.7)	4 (5.7)	8 (5.7)
Back pain	1 (1.4)	7 (10.0)	8 (5.7)
Bone pain	1 (1.4)	3 (4.3)	4 (2.9)
Myalgia	4 (5.7)	2 (2.9)	6 (4.3)
Nervous system disorders	19 (27.1)	25 (35.7)	44 (31.4)
Headache	3 (4.3)	3 (4.3)	6 (4.3)
Hypoaesthesia	5 (7.1)	0	5 (3.6)
Neuropathy peripheral	10 (14.3)	12 (17.1)	22 (15.7)
Paraesthesia	3 (4.3)	8 (11.4)	11 (7.9)
Psychiatric disorders	2 (2.9)	8 (11.4)	10 (7.1)
Insomnia	0	6 (8.6)	6 (4.3)
Respiratory, thoracic and mediastinal disorders	8 (11.4)	9 (12.9)	17 (12.1)
Cough	1 (1.4)	3 (4.3)	4 (2.9)
Dyspnoea	3 (4.3)	1 (1.4)	4 (2.9)
Oropharyngeal pain	0	3 (4.3)	3 (2.1)
Skin and subcutaneous tissue disorders	16 (22.9)	12 (17.1)	28 (20.0)
Alopecia	10 (14.3)	5 (7.1)	15 (10.7)
Rash	3 (4.3)	1 (1.4)	4 (2.9)
Vascular disorders	6 (8.6)	4 (5.7)	10 (7.1)
Hypertension	3 (4.3)	1 (1.4)	4 (2.9)
Thrombophlebitis	0	3 (4.3)	3 (2.1)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED, CSR Table 14.3.1.1. Some Preferred Terms (PTs) were combined. See Appendix Section Summary of Clinical Safety 2.7.4.7.1 for further details.

Overall, Grade 3 or higher TEAEs were more frequent in the CT-P10 group. Twenty-six (37.1%) and 20 (28.6%) patients experienced one or more Grade 3 or higher TEAE in the CT-P10 and Rituxan arms, respectively. Notably, Grade 3 or higher neutropenia was more frequent in the CT-P10 group (25.7% vs. 15.7% Rituxan group) as was pneumonia (5.7% vs 0% in the Rituxan group). These Grade 3 or higher TEAEs are summarized by SOC and PT in Table 19. The number (%) of patients who experienced at least 1 TEAE of febrile neutropenia was 2 (2.9%) patients in both treatment groups.

Table 19. Summary of ≥Grade 3 TEAEs (≥3% of Patients by PT in Either Treatment Group) in CT-P10 3.3 (Part 2): Safety Population

System Organ Class Preferred Term	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)	Total (N=140) n (%)
Number (%) of patients with ≥ 1 ≥Grade 3 TEAEs	26 (37.1)	20 (28.6)	46 (32.9)
Blood and lymphatic system disorders			
Neutropenia	18 (25.7)	11 (15.7)	29 (20.7)
Infections and infestations			
Pneumonia	4 (5.7)	0	4 (2.9)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED. Some Preferred Terms (PTs) were combined. See Appendix Section Summary of Clinical Safety 2.7.4.7.1 for further details.

Reviewer comment: All-grade neutropenia and Grade 3 or higher neutropenia were more frequent in the CT-P10 arm. Of note, more patients in the CT-P10 treatment group had bone marrow involvement at baseline (45 [64.3%] patients in the CT-P10 treatment group versus 33 [47.1%] patients in the Rituxan treatment group). Furthermore, among the patients with TEAE of neutropenia, 18 patients in the CT-P10 treatment group and 7 patients in the Rituxan treatment group had bone marrow involvement at baseline. This suggests that the observed differences in incidence of neutropenia may be attributable to differences in baseline bone marrow involvement.

7.4.2 Laboratory Findings

Blood samples (including samples for beta-2 microglobulin) and urine samples for clinical laboratory assessments were collected at the time points specified in the s.

Blood samples were not collected in a fasting state unless, in the opinion of the investigator, fasting blood samples were required.

A serum pregnancy test (local laboratory) was conducted at screening and at both the EOT visits, and then a urine pregnancy test for women of childbearing potential who had not been surgically sterilized was used to confirm that patients were not pregnant before dosing on Day 1 of each cycle in the Core Study Period and Maintenance Study Period.

Figure 4 illustrates the laboratory analyses that were performed:

Figure 4. Laboratory Analyses

Hematology	Clinical Chemistry	Urinalysis
• Absolute neutrophil count • Hemoglobin • Platelets • White blood cell count	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen • Calcium • Creatinine • Glucose • Lactate dehydrogenase • Potassium • Sodium • Total bilirubin • Total protein • Uric acid	• Bilirubin • Blood • Glucose • Ketones • Protein • Microscopic examination of white blood cell count, red blood cell count, and bacteria, <i>only if urinalysis dipstick results for any of the analytes are 2+ or greater</i>

Source: CSR 9.5.1.5.2

Reviewer comment: There were no reported cases of HBV activation in Study CT-P10 3.3.

7.4.3 Vital Signs

Vital signs and weight were collected at the screening period, Day 1 of each cycle and EOT1 during the Core Study Period, and Day 1 of each cycle and EOT2 during the Maintenance Study Period. Mean changes from baseline were small for vital signs. No notable differences were observed between the treatment groups in CT-P10 3.3.

7.4.4 Electrocardiograms (ECGs)

All scheduled 12-lead ECGs were performed (screening period; after the 4th cycle and EOT1 after the Core Study Period; after the 3rd, 6th, 9th cycles and EOT2 in the Maintenance Study Period) after the patient had rested quietly for at least 5 minutes in

the supine position. If, following ECG review by the investigator, there were any ECG findings that indicated cardiac insufficiency or QT prolongation, the patient was referred to a cardiologist and the findings were recorded in both the source documents and the eCRF

Mean changes from baseline were small for ECGs. No notable differences were observed between the treatment groups in CT-P10 3.3.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies for similarity of safety endpoints submitted for review.

7.4.6 Immunogenicity

Please refer to detailed review of immunogenicity by Dr. Haoheng Yan. Briefly, the ADA binding assay and the NAb assay are inadequate for use in this study (CT-P10 3.3), because the assay sensitivity (drug tolerance) is inadequate under the higher serum drug concentrations seen in the study. The ADA and NAb rates are likely under-reported for all of the sample points.

Table 20. Summary of Testing for ADA and NAb Up to Core Cycle 8 [24 Weeks] in Study CT-P10 3.3 (Part 2): Safety Population

Immunogenicity Test	CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)
Screening		
ADA Positive	5 (7.1)	8 (11.4)
Nab Positive (as % of ADA positive)	0	0
Core Cycle 4		
ADA Positive	2 (2.9)	1 (1.4)
Nab Positive (as % of ADA positive)	2 (100)	1 (100)
EOT1		
ADA Positive	1 (1.4)	1 (1.4)
Nab Positive (as % of ADA positive)	0	1 (100)

Source: Integrated Summary of Immunogenicity Table 36

Reviewer Comment: ADA and/or NAb results were similar in the two treatment groups up to Core Cycle 8. The majority of patients had negative ADA results, though these findings should be considered in the context of the assay inadequacies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

There were no clinically meaningful differences in safety according to demographic factors, including age, gender, and race. Table 21 summarizes the frequency of one or more TEAE in Study CT-P10 3.3.

Table 21. Number (%) of patients with ≥ 1 TEAE by Age, Gender and Race in Study CT-P10 3.3: Safety Population

		CT-P10 (N=70) n (%)	Rituxan (N=70) n (%)
Age	< 65 years	42/51 (82.4)	38/49 (77.6)
	≥ 65 years	16/19 (84.2)	18/21 (85.7)
Gender	Male	25/30 (83.3)	28/33 (84.8)
	Female	33/40 (82.5)	28/37 (75.7)
Race	White	41/51 (80.4)	39/52 (75.0)
	Asian	11/11 (100.0)	12/13 (92.3)
	Others¹	6/8 (75.0)	5/5 (100.0)

Source: Summary of Clinical Safety 2.7.4-45

¹ This includes Mestizo/Mestiza, Mixed and other races.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

No human or animal studies have investigated the potential effects of CT-P10 during pregnancy and lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

No human studies have investigated the potential effects of CHS-1701 in pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential effects of CT-P10 overdose have not been systematically studied.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

CT-P10 was approved in South Korea in November 2016 and in the EU in February 2017 under the proprietary name TRUXIMA. No postmarket safety was provided in this application. There are no potential safety concerns regarding subpopulations. There are no specific safety concerns that could be expected from anticipated off-label use.

9 Appendices

9.1 Literature Review/References

(1) cancer.gov

9.2 Labeling Recommendations

Labeling review is still pending at the time of this review.

9.3 Advisory Committee Meeting

At the time of this review, an Advisory Committee Meeting is not planned.

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/s/

ANAND SHAH
12/03/2017

NICOLE J GORMLEY
12/05/2017