

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
October 10, 2018

DRAFT QUESTIONS

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

Proposed Indications:

Treatment of adult patients with

1. Relapsed or refractory, low grade or follicular, CD20-positive, B-cell Non-Hodgkin's Lymphoma (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.

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

Background

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product.

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Summary of FDA Review

Data	Source
Analytical similarity	➤ Pairwise comparisons between US-licensed Rituxan and CT-P10 lots.
Nonclinical pharmacology and toxicology	➤ Comparative 8-week repeat-dose toxicity study in cynomolgus monkeys ➤ Tissue cross-reactivity study (human tissues)
Immunogenicity	➤ CT-P10 3.2: Randomized, double-blind, active-controlled, parallel group study in patients with rheumatoid arthritis
Clinical Pharmacology	➤ CT-P10 3.2: Randomized, double-blind, active-controlled, parallel group study in patients with rheumatoid arthritis ➤ CT-P10 3.3: Randomized, double-blind, active-controlled, parallel group study in patients with advanced follicular lymphoma ➤ CT-P10 3.4: Randomized, double-blind, active-controlled, parallel-group study in patients with low tumor burden follicular lymphoma
Clinical Safety and Efficacy	➤ CT-P10 3.3: Randomized, double-blind, active-controlled, parallel group study in patients with advanced follicular lymphoma ➤ CT-P10 3.4: Randomized, double-blind, active-controlled, parallel-group study in patients with low tumor burden follicular lymphoma

Analytical Similarity: CT-P10 is a proposed biosimilar to US-licensed Rituxan. The Applicant used an array of analytical methods to assess the primary, secondary and higher order structure, physicochemical properties, and biological functions of CT-P10 in comparison to US-licensed Rituxan.

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

Pharmacology/Toxicology: The Applicant submitted two nonclinical studies in support of this BLA. The primary nonclinical study was a comparative 8-week repeat-dose toxicity study in

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cynomolgus monkeys. The toxicity, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of CT-P10 were acceptable.

Immunogenicity: The incidence of immunogenicity for CT-P10 and US-Rituxan was compared in a multiple-dose, parallel-arm study in subjects with rheumatoid arthritis (Study CT-P10 3.2). Study CT-P10 3.2 was designed as a PK similarity study (Part 1), a comparative clinical study (Part 2), and a study to assess safety and immunogenicity in patients undergoing a single transition from US-licensed Rituxan to CT-P10 (Part 3). FDA determined that the comparative immunogenicity data from Study CT-P10 3.2 was sufficient to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

Clinical Pharmacology: The Applicant submitted Study CT-P10 3.2 to support PK similarities of CT-P10 and US-licensed Rituxan. Pharmacokinetic data from Study CT-P10 3.3, Part 1 and Study CT-P10 3.4 were also submitted and are considered as supportive.

The 90% confidence intervals (CI) for the ratio of geometric means for the pairwise comparisons of AUC_{0-14d}, AUC_{0-t}, and AUC_{0-∞} were within the pre-specified limits of 80 – 125%. The results of study CT-P10 3.2 established PK similarity between CT-P10 and US- licensed Rituxan. For Study CT-P10 3.3 and Study CT-P10 3.4, the PK results of CT-P10 were comparable to the PK results of US-Rituxan.

Efficacy/Safety: The Applicant submitted two clinical studies that compared CT-P10 to US-Rituxan in the oncology setting. Both studies were randomized, double-blinded, parallel group studies that enrolled subjects with either advanced follicular lymphoma (Study CT-P10 3.3) or low tumor burden follicular lymphoma (Study CT-P10 3.4). The FDA review of the data from both studies supports the Applicant's conclusion that there are no clinically meaningful differences between CT-P10 and US-licensed Rituxan.

QUESTIONS:

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

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4. **VOTE:** Does the totality of the evidence support licensure of CT-P10 as a biosimilar product to US-licensed Rituxan for the following indications:

Treatment of adult patients with

- a. relapsed or refractory, low-grade or follicular, CD20-positive, B-cell Non-Hodgkin's Lymphoma (NHL) as a single agent
- b. 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
- c. 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