CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761377Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 147335

MEETING PRELIMINARY COMMENTS

Celltrion, Inc.
c/o Parexel, International
Attention: Ally Danta
Senior Associate
2520 Meridian Pkwy, Suite 200
Durham, NC 27713

Dear Ms. Danta:

Please refer to your investigational new drug application (PIND) file for CT-P42. We also refer to your October 31, 2022, correspondence, received on October 31, 2022, requesting a meeting to reach an agreement with the FDA on the format and structure of a proposed (b) (4) biosimilar product application for CT-P42 to be submitted under Section 351(k) of the PHS Act.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, call me at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, MA
Senior Regulatory Project Manager
Ophthalmology
Division of Regulatory Operations
for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: January 31, 2023; 4:00-5:00 PM EST
Meeting Location: Teleconference

Application Number: 147335
Product Name: CT-P42

Indication: CT-P42 is being developed for the same indications as those approved for US-licensed Eylea

Sponsor Name: CELLTRION, Inc.

FDA ATTENDEES

Wiley Chambers, MD	Director, Division of Ophthalmology (DO)
William Boyd, MD	Deputy Director DO
Rhea Lloyd, MD	Clinical Team Leader
Mukesh Summan, PhD	Director, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Ping Ji, PhD	Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Soo Hyeon Shin, PharmD, PhD	Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Greg Soon, PhD	Statistics Team Leader, Office of Biometrics/Division of Biometrics IV (OB/DBIV)
Yan Zhou, PhD	Statistician, OB/DBIV
Sam Mindaye, PhD	Review Chief, Office of Biotechnology Product (OBP)/ Division of Biotechnology Review and Research IV (DBRRIV)
Leiyun Boone, PhD	Product Quality Reviewer, OPQ/OBP/DBRRIV
Marlene Schultz-Depalo, M.S., M.A., RAC	OBP Biosimilar Program and Policy Analyst
Carol Kim	
Emanuela Lacana, PhD	Deputy Director, OTBB, OND
Nina Brahme, PhD, MPH	Scientific Reviewer, OTBB, OND
Carol Kim, Pharm.D.	Scientific Reviewer, OTBB, OND

Thomas Herndon	
Jacquelyn Smith, MA	Senior Project Manager, Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Specialty Medicine (DROSM)
Murewa Oguntimein, PharmD	Program Coordinator, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis I (DMEPA I)
Sofanit Getahun, PharmD	Safety Evaluator, OSE/OMEPRM/DMEPAI

SPONSOR ATTENDEES

JaeHwee Park	Head of Regulatory Affairs Division
IlSung Chang	Head of Biometrics Department
JongHwan Kim	Head of Clinical Regulatory Affairs Department
MinKyoung Jeon	Head of Regulatory Affairs Department
Bianca Park	Team Leader of Clinical Regulatory Affairs 1
YuMi Kim	Team Leader of Regulatory Affairs 3
SangMi Lee	Team Leader of Clinical Statistics 4
JiMin Song	Assistant Manager of Clinical Regulatory Affairs 1
JeongSoo Hong	Assistant Manager of Regulatory Affairs 3

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 31, 2023, between Celltrion Inc. and the Division of Ophthalmology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Mylan Pharmaceuticals Inc. and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

1.0 BACKGROUND

Celltrion, Inc. has requested a meeting to discuss their CT-P42 product. Celltrion's questions are provided in **bold** print. FDA's responses to these questions are provided in *italic* font. The discussion begins below.

2.0 DISCUSSION

Administrative

1. **Does the FDA agree with the list of documents to be submitted in Module 1 of the initial Biologics License Application (BLA) for CT-P42*, a proposed* (b) (4) ***biosimilar to*** **US-Eylea, under section 351(k)?**

Specifically, would the FDA agree with the Sponsor's approach to (b) (4) **?**

Agency Response: *Acceptable.*

Non-Clinical Program

2. **For the initial 351(k) BLA, CELLTRION intends to submit nonclinical study results including *in vitro* pharmacodynamic similarity studies and a 12-week repeat-dose toxicity study conducted in cynomolgus monkeys where toxicokinetics (TK) has been evaluated as well. The full toxicology study report including the TK study results will be also provided in Section 4.2.3.2. Along with this, nonclinical overview and summary of the nonclinical data will be also provided. CELLTRION believes that it is sufficient to submit the complete Nonclinical Overview (Section 2.4), the Pharmacokinetics Written Summary (Section 2.6.4), the Pharmacokinetics Tabulated Summary (Section 2.6.5), the Toxicology Written Summary (Section 2.6.6) and the Toxicology Tabulated Summary (Section 2.6.7). The other sections of the Nonclinical Summary (Sections 2.6.1-2.6.3) will also be submitted in order to have a complete dossier in CTD but the location of module where the relevant information is located will be only cited.**

Is this approach of presenting the nonclinical information in Modules 2 and 4 acceptable for the FDA?

Agency Response: Your proposed approach is acceptable.

Clinical Program

3. **In line with FDA's recommendations, CELLTRION is currently conducting a Phase 3 clinical study (CT-P42 3.1) to demonstrate similarity between CT-P42 and Eylea. CELLTRION is of the opinion that submission of all clinical summary sections would not be sensible when there is only a single study and for that reason, CELLTRION believes that it is sufficient to submit the complete Clinical Overview (Section 2.5), the Summary of Biopharmaceutics and Associated Analytical Methods (Section 2.7.1) and the Integrated Summary of Immunogenicity (ISI) (Section 2.7.2.4) together with the full clinical study report for Study CT-P42 3.1 (Section 5.3.5.1). These sections will contain all the information about the clinical development of the biosimilar product. In Sections 2.7.2, 2.7.3 and 2.7.4, the location of module where the relevant information is located will be only cited. The corresponding tables, figures and dataset will be provided in Section 5.3.5.3 in any case.**

Is this approach of presenting the clinical information in Modules 2 and 5 acceptable for the FDA?

Agency Response: Acceptable.

4. **In the initial 351(k) BLA, CELLTRION will also submit SAS program codes used to produce the PK, efficacy and safety (in relation to adverse events and immunogenicity only) analysis results presented in the study reports of the comparative clinical study but SAS program codes for the other analyses, including post-hoc analyses and other safety analyses, will be excluded from the initial 351(k) BLA package.**

Does the Agency agree with the proposed approach?

Agency Response: Your proposed approach is acceptable.

3.0 OTHER COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA III. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application

components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on the Program is available at FDA.gov.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, Questions and Answers on Biosimilar Development and the BPCI Act.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional

guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans3. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

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/

JACQUELYN E SMITH
01/04/2023 11:16:53 AM