U.S. FOOD & DRUG ADMINISTRATION

BLA 761338/Original 2

PROVISIONAL DETERMINATION

CELLTRION, Inc.
c/o Parexel International
Attention: Ally Danta
Regulatory Affairs Consultant
2520 Meridian Parkway, Suite 100
Durham, NC 27713

Dear Ally Danta:

Please refer to your biologics license application (BLA) dated and received June 30, 2023, and your amendments, submitted under section 351(k) of the Public Health Service (PHS) Act for Steqeyma (ustekinumab-stba) injection. We acknowledge receipt of your resubmission dated October 16, 2024, which constituted a complete response to our September 30, 2024, action letter.

BLA 761338 seeks licensure of:

- Steqeyma (ustekinumab-stba) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as interchangeable with Stelara (ustekinumab) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use,

- Steqeyma (ustekinumab-stba) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as interchangeable with Stelara (ustekinumab) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use, and

- Steqeyma (ustekinumab-stba) injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL single-dose vial for intravenous use.

This BLA proposes the use of Steqeyma (ustekinumab-stba) injection for adult and pediatric patients 6 years and older with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy, adult and pediatric patients 6 years and older with active psoriatic arthritis (PsA), adult patients with moderately to severely active Crohn's disease (CD), and adult patients with moderately to severely active ulcerative colitis.

For administrative purposes, we have split BLA 761338 as follows:

- BLA 761338/Original 1 – biosimilarity
- BLA 761338/Original 2 – interchangeability

The subject of this correspondence is BLA 761338/Original 2. A separate correspondence was issued for BLA 761338/Original 1.

All future submissions to these BLAs should specify the BLA number and the Original number to which each submission pertains.

We have completed a provisional review of this application, as amended. A final determination under sections 351(i) and 351(k) of the PHS Act that:

- Steqeyma (ustekinumab-stba) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use would be interchangeable with Stelara (ustekinumab) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use

- Steqeyma (ustekinumab-stba) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use would be interchangeable with Stelara (ustekinumab) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use

- Steqeyma (ustekinumab-stba) injection 130 mg/26 mL single-dose vial for intravenous use would be interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL single-dose vial for intravenous use

is currently subject to unexpired exclusivity for the first interchangeable biosimilar biological products, and thus may not be made before the exclusivity has expired. See section 351(k)(6) of the PHS Act. We have not identified any deficiencies that would justify a complete response action at this time; however, we also cannot approve your application because of the unexpired first interchangeable exclusivity. We have therefore provisionally determined that your 351(k) application meets the interchangeability criteria under section 351(k) of the PHS Act.

This provisional determination is based upon information available to the Agency at this time (i.e., information in your application and that the manufacturing of the biological product complies with the standards established in the BLA as well as the requirements in applicable regulations). This determination is subject to change on the basis of any new information that may come to our attention.

To obtain approval of this application, submit an amendment no more than six months prior to the date you believe that your application will be eligible for approval. In your cover letter, clearly identify your amendment as **"REQUEST FOR APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for approval and should include a copy of any relevant supporting documentation, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in

your cover letter. Any changes require our review before approval, and the goal date for our review will be set accordingly.

BLA 761338/Original 2 is not approved and Steqeyma (ustekinumab-stba) cannot be legally marketed as an interchangeable biosimilar product unless and until you have been notified in writing that BLA 761338/Original 2 is approved after any necessary additional review. Enclosed are the currently agreed upon labeling (text for the Prescribing Information, Medication Guide, Instructions for Use, Carton and Container labeling). If you believe that there are grounds for issuing the approval letter before the expiration of the exclusivity period, you should amend your application accordingly.

REQUIRED PEDIATRIC ASSESSMENTS

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 an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Refer to the "Required Pediatric Assessments" section of the correspondence for BLA 761338/Original 1.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4765-2: Repeat the bacterial retention study [(b) (4)] with CT-P43 drug product (5 mg/mL) to verify that the bacterial retention performance [(b) (4)] is not impacted by contact with the drug product solution [(b) (4)]

The timetable you submitted on December 10, 2024, states that you will conduct this study according to the following schedule:

Final report submission: 03/2025

Submit clinical protocols to your IND 146085 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

If you have any questions, email H. F. Van Horn III, PharmD, MBA, Senior Regulatory Project Manager, at Howard.VanHornIII@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

50 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

TATIANA OUSSOVA
12/17/2024 03:57:46 PM

U.S. FOOD & DRUG ADMINISTRATION

BLA 761338

COMPLETE RESPONSE

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

Dear Ally Danta:

Please refer to your biologics license application (BLA) dated and received June 30, 2023, submitted under section 351(k) of the Public Health Service Act for CT-P43.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY MICROBIOLOGY

(1) The bacterial retention study is inadequate (b) (4) (b) (4) for the CT-P43 drug product, 130 mg/26 mL (5 mg/mL) single-dose vial for IV use. (b) (4) (b) (4) (b) (4) Repeat the bacterial retention study of the (b) (4) for CT-P43 drug product, 130 mg/26 mL (5 mg/mL) single-dose vial for IV use.

(2) The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 drug product, 130 mg/26 mL (5 mg/mL) single-dose vial for IV use is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA guidance for industry *"Analytical Procedures and Methods Validation for Drugs and Biologics (2015)"*, for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all

samples by spectrophotometry and provide an updated method description with acceptance criteria and submit additional method validation data accordingly.

PRODUCT QUALITY

(3) The proposed release and stability specification for clarity of [redacted] for CT-P43 drug product (DP) [SCS] is not acceptable because it is not justified by your clinical and manufacturing experience. In your response to information request (IR), received on May 13, 2024, you proposed not to tighten this release and stability specification based on [redacted] for Lot No. 2NGP01 as justification. The proposed justification is not acceptable as it is not clinically relevant. Results from [redacted] should not be used to support the release and long-term stability acceptance criteria. In addition, this specification is not supported by the updated full term (36 months) stability data from the primary stability (non-PPQ) batches provided in the same amendment in SN 0027, which consistently showed results are below [redacted] NTU at all timepoints throughout the product shelf life. Tighten the release and stability acceptance criteria for clarity for CT-P43 [SCS] DP based on the historical release and long-term stability results to ensure consistent quality of CT-P43 DP [SCS].

(4) The proposed shelf-life limit of [redacted] in CT-P43 45 mg/0.5 mL and 90 mg/mL PFS and 130 mg/26 mL (5 mg/mL) Vial DP is not supported by your clinical and manufacturing experience. In the IR response received on May 13, 2024, you proposed not to tighten this shelf-life limit based on [redacted] You described that the [redacted] are associated with an [redacted] However, the proposed shelf-life limit does not reflect the clinical and manufacturing experience and is not supported by the updated full term stability results (all data points ≤ [redacted]%) from the primary stability batches (non-PPQ) for both 45 mg/0.5 mL and 90 mg/mL PFS and 130 mg/26 mL (5 mg/mL) vial DP presentations provided in the same amendment in SN 0027. Tighten the shelf-life acceptance criteria for [redacted] based on long term stability data to ensure the consistent CT-P43 DP quality over the shelf-life.

PRESCRIBING INFORMATION

(5) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry "*Labeling for Biosimilar Products"*.

CARTON AND CONTAINER LABELING

(6) We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

(7) Please refer to correspondence dated, September 29, 2023, which addresses the proposed proprietary name, Steqeyma. This name was found conditionally acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the US-licensed reference product.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.
- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

PRODUCT QUALITY MICROBIOLOGY

(1) The sensitivity of the dye ingress method used to demonstrate container closure integrity (CCI) (b) (4) is unclear. Additional information is needed to confirm that the (b) (4) parameters will result in integral vials. The method description in section 3.2.P.2.5.4 states that (b) (4) If not, provide additional CCI test results from vials (b) (4) The method used during (b) (4) should be demonstrated to be sensitive enough to detect breaches that could allow microbial ingress (≤20 microns).

(b) (4)

(b) (4)

(3) The acceptance criteria for the post-use integrity test of the (b) (4) for the 130 mg/26 mL (5 mg/mL) single-dose vial CT-P43 drug product listed in section 3.2.P.3.4 are based on the (b) (4) (b) (4) Update section 3.2.P.3.4 with the (b) (4) (b) (4) prior to integrity testing, as (b) (4) product could impact results of the test. The post-use integrity test result should be accurate to support sterility assurance of the product.

(4) The sterilization validation summary for stoppers used for the 130 mg/26 mL (5 mg/mL) single-dose vial CT-P43 drug product does not specify the actual sterilization parameters used during the studies. The sterilization validation parameters are needed to ensure that a sterility assurance level of 10-6 is demonstrated for the stoppers. (b) (4) (b) (4)

(5) It is unclear whether the depyrogenation/sterilization validation studies for glass vials were designed to evaluate the worst-case locations in the (b) (4) (b) (4)

(6) Additional (b) (4) results to validate the (b) (4) for the 130 mg/26 mL (5 mg/mL) single-dose vial CT-P43 drug product at (b) (4) were planned to be submitted by June 25, 2024, however these results were not reviewed. In the resubmission, provide summary data from at least one media fill run with the container closure system of the 130 mg/26 mL (5 mg/mL) single-dose vial CT-P43 drug product to support validation of the (b) (4)

(b) (4)

(b) (4)

Product Quality

Drug Substance

(b) (4)

Drug Product

(9) As indicated in the proposed labeling, individual pre-filled syringes or vials may be stored at room temperature up to 30 °C for a maximum single period of up to (b) (4) days in the carton. You provided the stability data under the accelerated 2 condition using representative DP lots to support the labeled in-use storage for CT-P43 at room temperature prior to administration or dilution. However, it appears end of shelf-life samples were not tested for in-use stability data under accelerated 2 condition. To ensure the in-use room temperature stability of the 130 mg/36 mL (5 mg/mL) single-dose vial, 45 mg/0.5 mL PFS, and 90 mg/mL PFS CT-P43 drug products, provide additional stability testing under the accelerated 2 condition using end of the shelf-life DP samples. In addition, to further support the in-use dilution stability of the 130 mg/26 mL single-dose vial CT-P43 drug product and as recommended per ICH Q1A(R2), provide additional in-use stability testing of end of shelf-life DP vial samples after the maximum (b) (4) days room temperature storage.

(10) We note that you only provided in-use compatibility study with (b) (4) IV bag. If you intend for the product to be used with other common bags such as (b) (4) or (b) (4) we recommend studies to support those.

(11) The information for some responses in Section 1.11.1 in SN 0027 received on May 13, 2024, was incomplete and/or inaccurate. For example, response to information request 4 was not submitted while response to information request 2 was submitted twice in Quality Information Amendment 2 and 4. Revise the quality information amendment to provide accurate and complete responses to the quality information request dated May 3, 2024, in your BLA re-submission.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under

21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products.*

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Susan Rhee, Chief of Project Management, at 301-796-2402 or susan.rhee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

TATIANA OUSSOVA
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