

BLA 761139/S-017
BLA 761139/S-020

**SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENT**

Daiichi Sankyo, Inc
Attn: Pranav Patel, PharmD
Manager, Regulatory Affairs Strategy
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Dr. Patel:

Please refer to your supplemental biologics license applications (sBLAs), dated and received November 17, 2021, as well as your amendments, submitted under section 351(a) of the Public Health Service Act for Enhertu (fam-trastuzumab deruxtecan-nxki) for injection.

These Prior Approval supplemental biologics license applications provide for the following:

- **Supplement 017:** Provides for regular approval of Enhertu (fam-trastuzumab deruxtecan-nxki) for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This indication initially received accelerated approval on December 20, 2019. We note that this indication is revised with S-020 and the final indication wording is reflected below.

- **Supplement 020:** Provides for modification of the breast cancer indication from:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

This indication was approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

to the following:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:

- in the metastatic setting, or
- in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling text for the Prescribing Information and Medication Guide, and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761139/S-017 and S-020.**”

Approval of this submission by FDA is not required before the labeling is used.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

You are exempt from this requirement for S-017 as none of the requirements apply. We are waiving the pediatric study requirement for S-020 because necessary studies are impossible or highly impracticable as breast cancer does not occur in the pediatric population.

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated November 17, 2021, reporting on the following postmarketing requirement listed in the December 20, 2019, approval letter for BLA 761139.

- 3762-1 Submit the final progression free survival analysis and datasets with the final report from a confirmatory Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a for HER2-positive, unresectable and/or metastatic breast cancer patients previously treated with trastuzumab, to confirm clinical benefit and provide additional efficacy data that may inform product labeling for fam-trastuzumab deruxtecan (DS-8201a).

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing commitments listed in the December 20, 2019, approval letter that are still open.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 4269-1 Conduct the interim and final OS analysis for clinical study DESTINY-Breast03 (NCT03529110) entitled “A Phase 3, multicenter, randomized, open-label, active-controlled study of T-DXd, an anti-HER2-antibody drug conjugate, versus T-DM1 for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane”, to further confirm the clinical benefit of T-DXd in this setting.

The timetable you submitted on April 6, 2022, states that you will conduct this study according to the following schedule:

Interim Report Submission:	04/2023
Trial Completion:	09/2026
Final Report Submission:	03/2027

Submit the final overall survival (OS) analysis and datasets with the final report.

Submit clinical protocols to your IND 127553 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**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Rashida Redd, Regulatory Project Manager, at 301-796-5489 or Rashida.Redd@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Carton and Container Labeling

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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/

LALEH AMIRI KORDESTANI
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