BLA 761139/S-028

ACCELERATED APPROVAL

Daiichi Sankyo, Inc.
Attention: Susie J Flores
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Susie J Flores:

Please refer to your supplemental biologics license application (sBLA), dated and received November 30, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Enhertu (fam-trastuzumab deruxtecan-nxki) 100 mg lyophilized powder for solution for intravenous injection.

This Prior Approval supplemental biologics license application provides for the use of Enhertu for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

This indication is 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 (Prescribing Information and

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 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-028**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 28, 2024. These requirements are listed below.

4624-1 Complete Cohort A in Part 2 of the ongoing DESTINY-PanTumor02 trial intended to verify and describe the clinical benefit of Enhertu in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options. Include a minimum of 40

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

patients across all tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer, including a sufficient number of patients with and representation of HER2-positive (IHC3+) tumor types that require additional characterization. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

Final Protocol Submission:	11/2023 (completed)
Trial Completion:	12/2026
Final Report Submission:	06/2027

Submit clinical protocols to your IND 149506 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each study and clinical trial required under section 506(c) (listed above) to this BLA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval of the original BLA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761139/S-028 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval of the original BLA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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.

We are waiving the pediatric studies requirement for ages 0 to <1 month old because necessary studies are impossible or highly impracticable due to the rarity of pediatric patients in this age group who would be eligible for investigational treatment with Enhertu.

We are deferring submission of your pediatric study for ages 1 month to < 17 years old for this application because additional pediatric nonclinical data are needed to inform the design of the pediatric clinical study.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4624-2 Conduct a clinical study of Enhertu to evaluate dosing, pharmacokinetics, safety, and efficacy of Enhertu in a sufficient number of pediatric patients ages 1 month to <17 years of age with unresectable or metastatic HER2-expressing solid tumors, that have progressed following prior treatment or who have no satisfactory alternative treatment options, deferred until results of completed or planned nonclinical in vitro and in vivo studies or available pediatric clinical data are submitted to and reviewed by FDA, and have been found to support a clinical investigation in the pediatric population.

Draft Protocol Submission	03/2026
Final Protocol Submission:	06/2026
Study Completion:	06/2032
Final Report Submission:	12/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit the protocol(s) to your IND 149506, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4624-3 Conduct a new pragmatic clinical trial with a sufficient number of patients to verify and describe the efficacy of Enhertu in adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors with disease that has progressed following prior treatment and have no satisfactory alternative treatment options. The trial should include a sufficient number of tumor types, other than breast, colorectal, lung, and gastric/GEJ cancer. In order to characterize response rate and duration of response, patients should be followed for at least 12 months from the onset of response.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2024
Final Protocol Submission:	02/2025
Trial Completion:	08/2028
Final Report Submission:	02/2029

Submit the datasets with the final report submission.

4624-4 Commitment to submit appropriate analytical and clinical validation study data using the DESTINY-PanTumor02, DESTINY-CRC02, and DESTINY-Lung01 clinical trials, to support labeling of an immunohistochemistry-based in-vitro diagnostic device that is essential for the safe and effective use of Enhertu for treatment of adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors.

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocol(s) to your IND 149506, with a cross reference letter to this BLA. 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 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

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[6]

[6] https://www.fda.gov/media/128163/download

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 Alice Lee, Senior Regulatory Project Manager, at (301) 796-8881 or at Alice.Lee@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

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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