BLA 761139/S-041
BLA 761139/S-043

SUPPLEMENT APPROVAL

Daiichi Sankyo, Inc.
Attention: Pranav J. Patel, PharmD
Associate Director, Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Patel:

Please refer to your supplemental biologics license applications (sBLAs) received on July 18, 2025, and January 7, 2026, and your amendments, submitted under section 351(a) of the Public Health Service Act for Enhertu® (fam-trastuzumab deruxtecan-nxki; herein referred to as T-DXd).

These Prior Approval sBLAs provide for two separate indications:

- ENHERTU followed by a taxane, trastuzumab, and pertuzumab (THP) is indicated for the neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer as determined by an FDA-authorized test;

- ENHERTU is indicated for the adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment.

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.

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 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 these sBLAs, including pending "Changes Being Effected" (CBE) supplements, for which the 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).

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 study(ies) requirement for these applications because necessary studies are impossible or highly impracticable, due to breast cancer rarely occurring in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[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.

For BLA 761139/S-041:

4997-1 Complete the ongoing clinical trial, DESTINY-Breast11 (DB-11), entitled "A Phase 3 Open-label Trial of Neoadjuvant Trastuzumab Deruxtecan (T-DXd) Monotherapy or T-DXd followed by THP Compared to ddAC-THP in Participants with High-risk HER2-positive Early-stage Breast Cancer", to provide the 3-year event free survival (EFS) and final overall survival (OS) analyses to fully characterize the clinical benefit of neoadjuvant T-DXd followed by THP compared to ddAC-THP in HER2-positive, Stage II and Stage III breast cancer, and EFS and OS for all T-DXd investigational arms of the trial compared to the ddAC-THP arm.

The timetable you submitted on April 27, 2026, states that you will conduct this study according to the following schedule:

Trial Completion:	04/2027
Interim Report Submission (3-year EFS):	11/2027
Final Report Submission (OS):	11/2027

For BLA 761139/S-043:

4998-1 Complete the ongoing clinical trial, DESTINY-Breast05 (DB-05), entitled "A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in subjects with high-risk HER2-positive primary breast cancer who have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy", to provide all additional IDFS, DFS and OS results, including at final IDFS analysis, and at the time of final analysis at trial completion to fully characterize the clinical benefit of adjuvant T-DXd compared to T-DM1 in HER2-positive, early-stage breast cancer at high risk of disease recurrence

The timetable you submitted on April 30, 2026, states that you will conduct this study according to the following schedule:

Interim Report Submission (IDFS final analysis):	09/2027
Trial Completion:	01/2028
Final Report Submission:	07/2028

Submit clinical protocols to your INDs 127553 (DB-05) and 146111 (DB-11) for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to these sBLAs. 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 these sBLAs. 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 in 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4]

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 Kim J. Robertson, Senior Health Regulatory Project Manager, at (301) 796-1441, or kim.robertson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information
    - Medication Guide

[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] 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
05/15/2026 03:59:12 PM