Dear Dr. Rusnak:

Please refer to your supplemental biologics license application (sBLA), dated and received February 16, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for ENHERTU (fam-trastuzumab deruxtecan-nxki) injection.

This Prior Approval sBLA provides for the use of ENHERTU (fam-trastuzumab deruxtecan-nxki) for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have an activating HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.

**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.

**WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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

**ACCELERATED APPROVAL REQUIREMENTS**

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 3, 2022. This requirement, along with required completion dates, is listed below.

These postmarketing clinical trials are subject to the reporting requirements of 21 CFR 601.70:

- **4321-1** Complete a clinical trial to obtain data on the clinical efficacy of fam-trastuzumab deruxtecan-nxki for the treatment of patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have an activating HER2 (ERBB2) mutation and have previously received systemic therapy, to provide a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response. This report will contain data from patients with NSCLC harboring HER2 mutations and data from at least 102 patients who have received prior systemic therapy, after all responders have been

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\(^1\) [http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm](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 at [https://www.fda.gov/RegulatoryInformation/Guidances/default.htm](https://www.fda.gov/RegulatoryInformation/Guidances/default.htm).

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followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

Draft Protocol Submission: 11/2022  
Final Protocol Submission: 02/2023  
Trial Completion: 09/2023  
Final Report Submission: 03/2024

4321-2  Conduct a multicenter, randomized clinical trial of fam-trastuzumab deruxtecan-nxki in patients with treatment-naïve, unresectable or metastatic non-small cell lung cancer whose tumors have an activating HER2 (ERBB2) mutation. The final analysis should include the final progression-free survival and overall survival results.

Final Protocol Submission: 07/2021 (completed)  
Trial Completion: 03/2028  
Final Report Submission: 09/2028

Submit clinical protocols to your IND 137009 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report 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.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “Subpart E Postmarketing Requirement(s).”

REQUARED 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 this application because necessary studies are impossible or highly impracticable.
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.\(^3\)

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 questions, contact Raniya Al-Matari at 301-796-1755, or email at Raniya.Al-Matari@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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\(^3\) [https://www.fda.gov/media/128163/download](https://www.fda.gov/media/128163/download)

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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/

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