CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761139Orig1s000

Trade Name:	ENHERTU
Generic or Proper Name:	fam-trastuzumab deruxtecan- nxki
Sponsor:	Daiichi Sankyo, Inc.
Approval Date:	December 20, 2019
Indication:	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.

CENTER FOR DRUG EVALUATION AND RESEARCH

761139Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761139Orig1s000

APPROVAL LETTER

BLA 761139

BLA ACCELERATED APPROVAL

Daiichi Sankyo, Inc.
Attention: Amita Chaudhari, MSc
Senior Director, Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Ms. Chaudhari:

Please refer to your biologics license application (BLA) dated August 29, 2019, received August 29, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for ENHERTU (fam-trastuzumab deruxtecan- nxki), 100mg for injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2128 to Daiichi Sankyo, Inc., Basking Ridge, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product ENHERTU (fam-trastuzumab deruxtecan-nxki). 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 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.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture MAAL-9001 drug substance intermediate at Daiichi Sankyo Chemical Pharma Co., Ltd. Tatebayashi Plant, Gunma, Japan and ENHERTU drug substance at Daiichi Sankyo Chemical Pharma Co, Ltd., Onahama Plant, in Fukushima, Japan. The final formulated product will be manufactured and filled at (b) (4) and labeled, and packaged at (b) (4)

(b) (4) You may label your product with the proprietary name ENHERTU and will market it as 100 mg lyophilized powder in a single-dose vial.

DATING PERIOD

The dating period for ENHERTU shall be 24 months from the date of manufacture when stored at 2-8° C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)° C. The dating period for your MAAL-9001 drug substance intermediate shall be (b) (4) months from the date of manufacture when stored at (b) (4)° C.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your MAAL-9001 drug substance intermediate, drug substance, and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ENHERTU to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of ENHERTU, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), 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] Content of labeling must be identical to the enclosed labeling (text for the

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

Prescribing Information and Medication Guide). 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.

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 (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761139**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for ENHERTU was not referred to an FDA advisory committee because evaluation of the data did not raise significant safety or efficacy issues in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials 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, 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 December 9, 2019. This requirement, along with required completion dates, is listed below.

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).

[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.

Final Protocol Submission:	05/2019 (completed)
Trial Completion:	12/2022
Interim Report (OS) Submission:	06/2023
Final Report Submission:	06/2023

Submit clinical protocols to your IND 127553 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)**."

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 this application because necessary studies are impossible or highly impracticable as breast cancer is rare in the pediatric population.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3762-2 Submit the integrated immunogenicity summary report for all patients with solid tumors in clinical studies treated with DS-8201a, including the ongoing Phase 3 trials, having an immunogenicity component. The final report should include anti-drug antibody (ADA) results from screening, confirmatory, titering, domain specificity, and neutralization assays, the results of linear or non-linear correlation analyses between ADA status and titers with PK, PD, efficacy, and safety (adverse event) data. Submit the Integrated Immunogenicity Summary Report in accordance with Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection.

The timetable you submitted on December 18, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

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

We remind you of your postmarketing commitments:

3762-3 Provide the bioburden test method qualification report for two additional batches of (b) (4) and DS-8201a drug substance in-process and release samples by May 2020.

The timetable you submitted on December 3, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2020

3762-4 Perform the microbial ingress container closure integrity test to validate the maximum and minimum crimping pressures and include a positive control with a breach size of ≤ 20 microns. In addition, monitor the viability of the challenge microorganism at the end of testing.

The timetable you submitted on December 3, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2020

3762-5 Provide data from a media fill run to support the use of the drug product specific container closure system.

The timetable you submitted on December 17, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2020

3762-6 Provide endotoxin method qualification using two (2) additional drug product batches manufactured at (b) (4).

The timetable you submitted on December 3, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2020

3762-7 Provide bioburden method qualification using 100 mL sample volumes from three (3) batches of DP manufactured at (b) (4).

The timetable you submitted on December 3, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2020

3762-8 Perform the dye ingress method validation for container closure integrity testing of the drug product stability samples using positive controls with a ≤20 micro breach size.

The timetable you submitted on December 3, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2020

3762-9 Improve the requalification procedures for the current (b) (4) primary reference standard (PRS) (b) (4) and secondary reference standard (SRS) (b) (4) by revising the requalification protocols to include numerical acceptance criteria for HER2 binding of the PRS and stability trending of additional quantitative quality attributes with pre-defined trending rules and criteria, to allow timely detection of changes in the quality attributes of the PRS and SRS and to inform when the current RSs should be replaced. The acceptance criteria for HER2 binding of the PRS, the selected quality attributes for trending, the trending rules and criteria, and the criteria for assessment of when the RSs should be replaced will be scientifically justified. The revised qualification protocol will be submitted to the Agency per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2020

3762-10 Improve the requalification procedures for the current DS-8201a primary reference standard (PRS) [redacted] and secondary reference standard (SRS) [redacted] by revising the requalification protocols to include numerical acceptance criteria for cell growth inhibition and HER2 binding activity, and stability trending of additional quantitative quality attributes with pre- defined trending rules and criteria, to allow timely detection of changes in the quality attributes of the PRS and SRS and to inform when the current RSs should be replaced. The numerical acceptance criteria for cell growth inhibition and HER2 binding activity, the selected quality attributes for trending, the trending rules and criteria, and the criteria for assessment of when the RSs should be replaced will be scientifically justified. The revised qualification protocols will be submitted to the Agency per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2020

3762-11 Confirm that the potency of the current DS-8201a primary reference standard [redacted] and secondary reference standard [redacted] is precise and accurate by conducting additional qualification of potency for primary reference standard [redacted] using a sufficient number of independent assays and replicates. The number of independent assays and replicates will be scientifically justified. The qualification data will be reported as per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2020

3762-12 Confirm that the potency of [redacted] primary reference standard [redacted] is precise and accurate by conducting additional qualification of potency of primary reference standard [redacted] using a sufficient number of independent assays and replicates. The number of independent assays and replicates will be scientifically justified. The qualification data will be reported as per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2020

3762-13 Strengthen the qualification of the current [redacted] (b) (4) primary and secondary reference standards by conducting additional characterization studies including full glycan profile analysis and FcγRIIIA binding activity of [redacted] (b) (4) primary reference standard [redacted] (b) (4) and secondary reference standard [redacted] (b) (4) to support the use of these reference standards in comparability assessments. The qualification data will be reported as per 21 CFR 601.12

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2020

3762-14 Strengthen the qualification of the DS-8201a primary and secondary reference standards by conducting characterization of FcγRIIIA binding activity for primary reference standard [redacted] (b) (4) to support the use of these reference standards in comparability assessments. The qualification data will be reported as per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2020

3762-15 Re-evaluate intermediate precision for the [redacted] (b) (4) protein concentration and glycan analysis methods at Daiichi Sankyo Tatebayashi Plant, and for protein concentration, non-proteinaceous impurities (NPI) and purity of payload (PoP) methods for DS-8201a drug substance at Daiichi Sankyo Onahama Plant and [redacted] (b) (4). The final report will be reported as per 21 CFR 601.12.

The timetable you submitted on December 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2020

3762-16 Develop and validate a neutralizing antibody assay to test confirmed anti-DS-8201a antibody positive samples from studies J101, J102, A103, A104, and U201 as well as the ongoing Phase 3 clinical studies U301, U302, and U303.

The timetable you submitted on December 18, 2019 states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2020

3762-17 Develop and validate domain specificity assays to test confirmed anti-DS-8201a antibody positive samples from studies J101, J102, A103, A104, and U201 as well as the ongoing phase 3 clinical studies U301, U302, and U303. Specifically, the assays should determine the specificity of anti-DS-8201a antibodies for the monoclonal antibody MAAL-9001, the drug MAAA-1181a, and the linker.

The timetable you submitted on December 18, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2020

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 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).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry.[3]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[4]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Sherry Hou, PharmD, Regulatory Project Manager, at 240-402-1813.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Deputy Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

[4] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

---

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/

MARC R THEORET
12/20/2019 12:00:00 AM