

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761139Orig1s021

Trade Name: ENHERTU

Generic or Proper Name: fam-trastuzumab deruxtecan-nxki

Sponsor: Daiichi Sankyo, Inc

Approval Date: August 11, 2022

Indication: Enhertu is a HER2-directed antibody and topoisomerase inhibitor conjugate 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.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective 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.

- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER



BLA 761139/S-021

ACCELERATED APPROVAL

Daiichi Sankyo, Inc.
Attention: David Rusnak, JD
Associate Director, Regulatory Affairs Strategy
211 Mount Airy Road
Basking Ridge, NJ 07920

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

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 at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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).**”

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 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

³ <https://www.fda.gov/media/128163/download>

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/

B HARPREET SINGH
08/11/2022 03:08:34 PM

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENHERTU safely and effectively. See full prescribing information for ENHERTU.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms. (2.3, 5.1)
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)

RECENT MAJOR CHANGES

Indications and Usage (1.1)	05/2022
Indications and Usage (1.2)	08/2022
Indications and Usage (1.3)	08/2022
Dosage and Administration (2.1)	08/2022
Dosage and Administration (2.2)	05/2022
Dosage and Administration (2.2)	08/2022
Dosage and Administration (2.3)	08/2022
Warnings and Precautions (5.1, 5.2, 5.3)	08/2022

INDICATIONS AND USAGE

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate 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. (1.1)
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. (1.2)
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. (1.3)

This indication is approved under accelerated approval based on objective 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. (1.3, 14.3)

- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. (1.4)

DOSAGE AND ADMINISTRATION

- Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine. (2.2, 2.4)
- For intravenous infusion only. Do not administer as an intravenous push or bolus. DO NOT use Sodium Chloride Injection, USP. (2.4)

- Premedicate for prevention of chemotherapy-induced nausea and vomiting. (2.2)
- The recommended dosage of ENHERTU for breast cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for lung cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for gastric cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU. (2.3)

DOSAGE FORMS AND STRENGTHS

For injection: 100 mg lyophilized powder in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Neutropenia: Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Manage through treatment interruption or dose reduction. (2.3, 5.2)
- Left Ventricular Dysfunction: Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF). (2.3, 5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥20%), including laboratory abnormalities, in patients with:

- metastatic breast cancer and HER2-mutant NSCLC were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, increased aspartate aminotransferase, vomiting, increased alanine aminotransferase, alopecia, increased blood alkaline phosphatase, constipation, musculoskeletal pain, decreased appetite, hypokalemia, diarrhea, and respiratory infection. (6.1)
- gastric cancer were decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, hypokalemia, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of ENHERTU. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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- 1.2 HER2-Low Metastatic Breast Cancer

- 1.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer
- 1.4 Locally Advanced or Metastatic Gastric Cancer

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.1)].**
- **Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1, 8.3)].**

1 INDICATIONS AND USAGE

1.1 HER2-Positive Metastatic Breast Cancer

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.

1.2 HER2-Low Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [see *Dosage and Administration* (2.1)].

1.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate and duration of response [see *Clinical Studies* (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Locally Advanced or Metastatic Gastric Cancer

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Unresectable or Metastatic HER2-Low Breast Cancer

Select patients for treatment of unresectable or metastatic HER2-low breast cancer with ENHERTU based on HER2 expression (IHC 1+ or IHC 2+/ISH-) [see *Clinical Studies* (14.2)].

Unresectable or Metastatic HER2-Mutant NSCLC

Select patients for the treatment of unresectable or metastatic HER2-mutant NSCLC with ENHERTU based on the presence of activating HER2 (ERBB2) mutations in tumor or plasma specimens [see *Clinical Studies* (14.3)]. If no mutation is detected in a plasma specimen, test tumor tissue.

Locally Advanced or Metastatic Gastric Cancer

Select patients with locally advanced or metastatic gastric cancer based on HER2 protein overexpression or HER2 gene amplification. Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.

Additional Patient Selection Information

Information on FDA-approved tests for the detection of HER2 protein expression, HER2 gene amplification, and activating HER2 mutations is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage and Schedules

Do not substitute ENHERTU for or with trastuzumab or ado-trastuzumab emtansine.

Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.

Permanently discontinue ENHERTU in case of severe infusion reactions.

Premedication

ENHERTU is moderately emetogenic [see *Adverse Reactions* (6.1)], which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of chemotherapy-induced nausea and vomiting.

Recommended Dosage for Metastatic Breast Cancer

The recommended dosage of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Recommended Dosage for Unresectable or Metastatic HER2-Mutant NSCLC

The recommended dosage of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Recommended Dosage for Locally Advanced or Metastatic Gastric Cancer

The recommended dosage of ENHERTU is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

2.3 Dosage Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU as described in Tables 1 and 2.

Do not re-escalate the ENHERTU dose after a dose reduction is made.

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.

Table 1: Dosage Reduction Schedule

Dose Reduction Schedule	Breast Cancer and NSCLC	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment.

Table 2: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Interstitial Lung Disease (ILD)/ Pneumonitis <i>[see Warnings and Precautions (5.1)]</i>	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt ENHERTU until resolved to Grade 0, then: - if resolved in 28 days or less from date of onset, maintain dose. - if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). - consider corticosteroid treatment as soon as ILD/pneumonitis is suspected.
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	- Permanently discontinue ENHERTU. - Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected.
Neutropenia <i>[see Warnings and Precautions (5.2)]</i>	Grade 3 (less than 1.0 to $0.5 \times 10^9/L$)	Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than $0.5 \times 10^9/L$)	- Interrupt ENHERTU until resolved to Grade 2 or less. - Reduce dose by one level (see Table 1).
Febrile Neutropenia <i>[see Warnings and Precautions (5.2)]</i>	Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature greater than $38.3^\circ C$ or a sustained temperature of $38^\circ C$ or greater for more than one hour	- Interrupt ENHERTU until resolved. - Reduce dose by one level (see Table 1).
Thrombocytopenia <i>[see Adverse Reactions (6.1)]</i>	Grade 3 (platelets less than 50 to $25 \times 10^9/L$)	Interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose.

Adverse Reaction	Severity		Treatment Modification
	Grade 4 (platelets less than $25 \times 10^9/L$)		- Interrupt ENHERTU until resolved to Grade 1 or less. - Reduce dose by one level (see Table 1).
Left Ventricular Dysfunction <i>[see Warnings and Precautions (5.3)]</i>	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		Continue treatment with ENHERTU.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	- Continue treatment with ENHERTU. - Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	- Interrupt ENHERTU. - Repeat LVEF assessment within 3 weeks. - If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. - If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		- Interrupt ENHERTU. - Repeat LVEF assessment within 3 weeks. - If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU.
	Symptomatic congestive heart failure (CHF)		Permanently discontinue ENHERTU.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v.5.0).

2.4 Preparation and Administration

In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is ENHERTU (fam-trastuzumab deruxtecan-nxki) and not trastuzumab or ado-trastuzumab emtansine.

Reconstitute and further dilute ENHERTU prior to intravenous infusion. Use appropriate aseptic technique.

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted ENHERTU solution required, and the number of vial(s) of ENHERTU needed *[see Dosage and Administration (2.2)]*.
- Reconstitute each 100 mg vial by using a sterile syringe to slowly inject 5 mL of Sterile Water for Injection, USP into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

- Dilute the calculated volume of reconstituted ENHERTU in an intravenous infusion bag containing **100 mL of 5% Dextrose Injection, USP**. DO NOT use Sodium Chloride Injection, USP. ENHERTU is compatible with an infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene).
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion, or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2°C to 8°C [36°F to 46°F]), allow the solution to reach room temperature prior to administration. Cover the infusion bag to protect from light.
- Administer ENHERTU as an intravenous infusion only with an infusion set made of polyolefin or polybutadiene.
- Administer ENHERTU with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix ENHERTU with other drugs or administer other drugs through the same intravenous line.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated.

3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of fam-trastuzumab deruxtecan-nxki as a white to yellowish white lyophilized powder in a single-dose vial for reconstitution and further dilution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU [see *Adverse Reactions* (6.1)]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery [see *Dosage and Administration* (2.3)]. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD [see *Dosage and Administration* (2.3)].

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

5.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction [see *Dosage and Administration* (2.3)].

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

5.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see *Dosage and Administration* (2.3)].

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see *Use in Specific Populations* (8.1), *Clinical Pharmacology* (12.1), *Nonclinical Toxicology* (13.1)]. Advise patients of the potential risks to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Neutropenia [see *Warnings and Precautions* (5.2)]
- Left Ventricular Dysfunction [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, 65% were exposed for greater than 6 months and 39% were exposed for greater than one year. In this pooled safety population, the most common ($\geq 20\%$) adverse reactions (including laboratory abnormalities) were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01.

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03 [see *Clinical Studies* (14.1)]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU and 7 months (range: 0.7 to 25) for patients who received ado-trastuzumab emtansine.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocyte count, increased alanine aminotransferase, decreased platelet count, fatigue, vomiting, increased blood

alkaline phosphatase, alopecia, hypokalemia, constipation, musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection, abdominal pain, increased blood bilirubin, and stomatitis.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast03.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast03

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	7	30	0.4
Vomiting	49	1.6	10	0.8
Constipation	34	0	20	0
Diarrhea	29	1.2	7	0.4
Abdominal pain ^a	21	0.8	8	0.4
Stomatitis ^b	20	0.8	5	0
Dyspepsia	11	0	6	0
General Disorders and Administration Site Conditions				
Fatigue ^c	49	6	35	0.8
Blood and Lymphatic System Disorders				
Anemia ^d	33	7	17	6
Skin and Subcutaneous Tissue Disorders				
Alopecia ^e	37	0.4	3.1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	31	1.2	25	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.6	17	0.4
Investigations				
Decreased weight	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Respiratory infection ^g	22	0.8	12	1.1
Epistaxis	11	0	16	0.4
Cough	11	0.4	10	0
Interstitial lung disease ^h	11	0.8	1.9	0
Nervous System Disorders				
Headache ⁱ	22	0.4	16	0
Peripheral neuropathy ^j	13	0.4	14	0.4
Dizziness	13	0.4	8	0

Events were graded using NCI CTCAE version 5.0.

- a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain
- b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption
- c Including fatigue, asthenia, malaise, and lethargy
- d Including anemia, decreased hemoglobin, and decreased red blood cell count
- e This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.
- f Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort
- g Including respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza-like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection
- h Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For ado-trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.
- i Including headache and migraine
- j Including peripheral neuropathy, peripheral sensory neuropathy, and paresthesia

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:

- *Respiratory, Thoracic and Mediastinal Disorders*: dyspnea (8%)
- *Skin and Subcutaneous Tissue Disorders*: pruritus (8%) and skin hyperpigmentation (6%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Nervous System Disorders*: dysgeusia (6%)
- *Metabolism and Nutrition Disorders*: dehydration (4.3%)
- *Eye Disorders*: blurred vision (3.5%)
- *Cardiac Disorders*: asymptomatic left ventricular ejection fraction decrease (2.7%) [see Warnings and Precautions (5.3)]
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (2.3%) [including hypersensitivity and infusion-related reactions]
- *Blood and Lymphatic System Disorders*: febrile neutropenia (0.8%)

Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	74	8	24	0.8
Decreased neutrophil count	70	18	30	2.3
Decreased hemoglobin	64	7	38	6
Decreased lymphocyte count	55	14	23	3.9
Decreased platelet count	52	7	79	24
Chemistry				
Increased aspartate aminotransferase	67	0.8	83	5
Increased alanine aminotransferase	53	1.6	67	6
Increased blood alkaline phosphatase	49	0.8	46	0.8
Hypokalemia	35	4.7	39	1.5
Increased blood bilirubin	20	0	14	0
Increased blood creatinine	16	0.8	8	0.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast01 and Study DS8201-A-J101

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900) [see *Clinical Studies (14.1)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were <65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, fatigue, vomiting, alopecia, increased aspartate aminotransferase, increased alanine aminotransferase, decreased platelet count, constipation, decreased appetite, diarrhea, hypokalemia, and cough.

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients in DESTINY-Breast01 and Study DS8201-A-J101.

Table 5: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	79	7
Vomiting	47	3.8
Constipation	35	0.9
Diarrhea	29	1.7
Abdominal pain ^a	19	1.3
Stomatitis ^b	14	0.9
Dyspepsia	12	0
General Disorders and Administration Site Conditions		
Fatigue ^c	59	6

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Skin and Subcutaneous Tissue Disorders		
Alopecia	46	0.4 ^d
Rash ^e	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	32	1.3
Blood and Lymphatic System Disorders		
Anemia ^f	31	7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	20	0
Dyspnea	13	1.3
Epistaxis	13	0
Interstitial lung disease ^g	9	2.6 ^h
Nervous System Disorders		
Headache ⁱ	19	0
Dizziness	10	0
Infections and Infestations		
Upper respiratory tract infection ^j	15	0
Eye Disorders		
Dry eye	11	0.4 ^k

Events were graded using NCI CTCAE version 4.03.

a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).

c Including fatigue and asthenia

d This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 2.

e Including rash, pustular rash, and maculo-papular rash

f Including anemia, decreased hemoglobin, decreased hematocrit, and decreased red blood cell count

g Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

h All events had fatal outcomes (n=6).

i Including headache, sinus headache, and migraine

j Including influenza, influenza-like illness, and upper respiratory tract infection

k This Grade 4 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for dry eye is Grade 3.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (2.6%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (1.7%)

Table 6: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU in DESTINY-Breast01 and Study DS8201-A-J101

Laboratory Parameter	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	70	7
Decreased hemoglobin	70	7
Decreased neutrophil count	62	16
Decreased platelet count	37	3.4
Chemistry		
Increased aspartate aminotransferase	41	0.9
Increased alanine aminotransferase	38	0.4
Hypokalemia	26	3

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

HER2-Low Metastatic Breast Cancer

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 [see *Clinical Studies (14.2)*]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, constipation, increased blood alkaline phosphatase, decreased appetite, musculoskeletal pain, diarrhea, and hypokalemia.

Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast04.

Table 7: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhea	27	1.3	22	1.7
Abdominal pain ^a	18	0.5	13	0
Stomatitis ^b	13	0.3	12	0.6
General Disorders and Administration Site Conditions				
Fatigue ^c	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0
Rash ^d	13	0	23	4.7
Blood and Lymphatic System Disorders				
Anemia ^e	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^f	32	1.3	31	0.6
Investigations				
Decreased weight	16	0.3	8	0
Vascular Disorders				
Hemorrhage ^g	16	0	3.5	0
Nervous System Disorders				
Headache ^h	15	0.3	6	0
Peripheral neuropathy ⁱ	13	0	29	5
Dizziness ^j	11	0.5	6	0
Infections and Infestations				
Upper respiratory tract infection ^k	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^l	12	1.3	0.6	0
Dyspnea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0.

a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation

c Including fatigue, asthenia, and malaise

d Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous

e Including anemia, decreased hemoglobin, and decreased red blood cell count

f Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain

g Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage

h Including headache and migraine

i Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia

j Including dizziness, postural dizziness, and vertigo

k Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis

l Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU:

- *Nervous System Disorders*: dysgeusia (10%)
- *Respiratory, Thoracic and Mediastinal Disorders*: cough (10%)
- *Gastrointestinal Disorders*: abdominal distension (5%), gastritis (2.7%), flatulence (2.4%)
- *Eye Disorders*: blurred vision (4.9%) [including blurred vision and visual impairment]
- *Skin and Subcutaneous Tissue Disorders*: pruritus (3.2%) and skin hyperpigmentation (2.7%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Metabolism and Nutrition Disorders*: dehydration (1.9%)
- *Blood and Lymphatic System Disorders*: febrile neutropenia (1.1%)
- *Injury, Poisoning and Procedural Complications*: infusion-related reactions (0.5%) [including injection site reaction and chills]

Table 8: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased white blood cell count	70	9	78	25
Decreased hemoglobin	64	8	53	6
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Hypokalemia	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

Unresectable or Metastatic HER2-Mutant NSCLC

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients in DESTINY-Lung02 [see *Clinical Studies (14.3)*]. Patients received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity. Nineteen percent of patients were exposed for greater than 6 months. The median age was 59 years (range 30 to 83); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued due to an adverse reaction in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, hypokalemia, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia.

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table 9: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	61	3.0
Constipation	31	1.0
Vomiting ^a	26	2.0
Diarrhea	19	1.0
Stomatitis ^b	12	0
Blood and Lymphatic System Disorders		
Anemia	34	10
General Disorders and Administration Site Conditions		
Fatigue ^c	32	4.0
Metabolism and Nutrition Disorders		
Decreased appetite	30	1.0
Skin and Subcutaneous Tissue Disorders		

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Alopecia	21	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^d	15	1.0

Events were graded using NCI CTCAE version 5.0.

a Including vomiting and retching

b including mucosal inflammation and stomatitis

c Including asthenia, fatigue, and malaise

d Including back pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Respiratory, Thoracic and Mediastinal Disorders*: interstitial lung disease (6%) [including interstitial lung disease that was adjudicated as ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure], dyspnea (5%), and epistaxis (3%)
- *Gastrointestinal Disorders*: abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- *Skin and Subcutaneous Disorders*: rash (3%) [including rash and maculo-papular rash]
- *Infections and Infestations*: upper respiratory tract infection (4%) [including upper respiratory tract infection, pharyngitis, and laryngitis]
- *Nervous System Disorders*: headache (4%) [including headache and migraine]

Table 10: Select Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=101 ^a	
	All Grades ^b %	Grades 3 or 4 ^b %
Hematology^c		
Decreased white blood cell count	60	4.0
Decreased hemoglobin	58	10
Decreased neutrophil count	52	12
Decreased lymphocyte count	43	16
Decreased platelet count	40	4.0
Chemistry		
Decreased albumin	39	0
Increased aspartate aminotransferase	35	1.0
Increased alanine aminotransferase	34	2.0
Increased alkaline phosphatase	22	0
Hypokalemia	17	2.0

a Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

b Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

c The denominator used to calculate the rate varied from 98 to 99 based on the number of patients with a baseline value and at least one post-treatment value.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see *Clinical Studies* (14.4)]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, hypokalemia, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia.

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 11: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

Adverse Reactions	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	63	4.8	47	1.6
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0
Abdominal pain ^a	14	0.8	15	3.2
Stomatitis ^b	11	1.6	4.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia ^c	58	38	31	23

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Adverse Reactions	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Febrile neutropenia	4.8	4.8	3.2	3.2
General Disorders and Administration Site Conditions				
Fatigue ^d	55	9	44	4.8
Pyrexia	24	0	16	0
Peripheral edema	10	0	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	22	0	15	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease ^e	10	2.4	0	0
Hepatobiliary Disorders				
Abnormal hepatic function	8	3.2	1.6	1.6

Events were graded using NCI CTCAE version 4.03.

^a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain

^b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering

^c Including anemia, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit

^d Including fatigue, asthenia, and malaise

^e Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- **Cardiac Disorders:** asymptomatic left ventricular ejection fraction decrease (8%) [see *Warnings and Precautions* (5.3)]
- **Infections and Infestations:** pneumonia (6%)
- **Injury, Poisoning and Procedural Complications:** infusion-related reactions (1.6%)

Table 12: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased hemoglobin	75	38	55	23
Decreased white blood cell count	74	29	53	13
Decreased neutrophil count	72	51	45	23
Decreased lymphocyte count	70	28	53	12
Decreased platelet count	68	12	12	5
Chemistry				
Increased aspartate aminotransferase	58	9	32	8

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Increased blood alkaline phosphatase	54	8	34	10
Increased alanine aminotransferase	47	9	17	1.7
Hypokalemia	30	4.8	18	8
Increased blood bilirubin	24	7	5	3.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (*see Data*). Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [*see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)*]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception

Females

ENHERTU can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose [see *Nonclinical Toxicology (13.1)*].

Infertility

Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.6% were 75 years or older. No overall differences in efficacy within clinical studies were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (60%) as compared to younger patients (48%).

Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

8.6 Renal Impairment

No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CLcr] ≥ 60 and < 90 mL/min) or moderate (CLcr ≥ 30 and < 60 mL/min) renal impairment [see *Clinical Pharmacology (12.3)*]. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment [see *Warnings and Precautions (5.1)*]. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr < 30 mL/min) [see *Clinical Pharmacology (12.3)*].

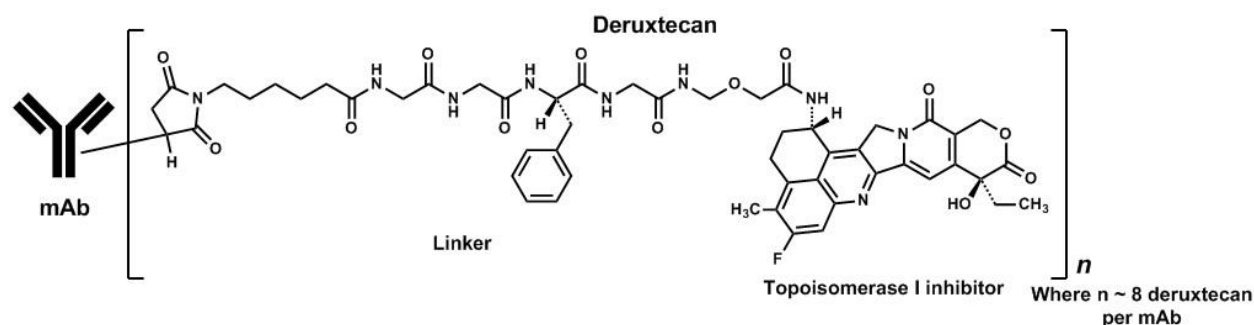
8.7 Hepatic Impairment

No dose adjustment of ENHERTU is required in patients with mild (total bilirubin $\leq$ ULN and any AST $>$ ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see *Dosage and Administration* (2.3)]. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody and topoisomerase inhibitor conjugate. Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb), covalently linked to 2) a topoisomerase inhibitor, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of a protease-cleavable maleimide tetrapeptide linker and the topoisomerase inhibitor, DXd, which is an exatecan derivative.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology, and the topoisomerase inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule. Fam-trastuzumab deruxtecan-nxki has the following structure:



ENHERTU (fam-trastuzumab deruxtecan-nxki) is a sterile, white to yellowish white, preservative-free lyophilized powder in single-dose vials. Each vial delivers 100 mg of fam-trastuzumab deruxtecan-nxki, L-histidine (4.45 mg), L-histidine hydrochloride monohydrate (20.2 mg), polysorbate 80 (1.5 mg), and sucrose (450 mg). Following reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration of fam-trastuzumab deruxtecan-nxki is 20 mg/mL with a pH of 5.5. The resulting solution is administered by intravenous infusion following dilution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody-drug conjugate. The antibody is a humanized anti-HER2 IgG1. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker. Following binding to HER2 on tumor cells, fam-trastuzumab deruxtecan-nxki undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The administration of multiple doses of ENHERTU 6.4 mg/kg every 3 weeks did not show a large mean effect (i.e. >20 ms) on the QTc interval in an open-label, single-arm study in 51 patients with metastatic HER2-positive cancer.

12.3 Pharmacokinetics

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki was evaluated in patients with cancer. Following a single dose, exposures ($C_{\max}$ and AUC) of fam-trastuzumab deruxtecan-nxki and released topoisomerase inhibitor (DXd) increased proportionally over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.6 to 1.5 times the recommended dose in breast cancer and NSCLC and 0.5 to 1.25 times the recommended dose in gastric cancer).

Metastatic Breast Cancer

At the recommended dosage of ENHERTU for patients with metastatic breast cancer, the geometric mean (coefficient of variation [CV]%) $C_{\max}$ of fam-trastuzumab deruxtecan-nxki and DXd were 133 $\mu\text{g/mL}$ (19%) and 4.7 ng/mL (43%), respectively, and the AUC of fam-trastuzumab deruxtecan-nxki and DXd were 780 $\mu\text{g}\cdot\text{day/mL}$ (27%) and 29 ng·day/mL (42%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 35% at steady-state (Cycle 3).

Unresectable or Metastatic HER2-Mutant NSCLC

At the recommended dosage of ENHERTU for patients with HER2-mutant NSCLC, the geometric mean (CV%) $C_{\max,ss}$ of fam-trastuzumab deruxtecan-nxki and DXd were 141 $\mu\text{g/mL}$ (21%) and 7.2 ng/mL (44%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki and DXd were 775 $\mu\text{g}\cdot\text{day/mL}$ (33%) and 40.9 ng·day/mL (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 31% at steady-state based on population pharmacokinetic analysis.

Locally Advanced or Metastatic Gastric Cancer

At the recommended dosage of ENHERTU for patients with HER2-positive gastric cancer, the geometric mean $C_{\max,ss}$ of fam-trastuzumab deruxtecan-nxki and DXd were 126 $\mu\text{g/mL}$ (18%) and 5.2 ng/mL (42%), respectively, and the AUC_{ss} of fam-trastuzumab deruxtecan-nxki and DXd were 743 $\mu\text{g}\cdot\text{day/mL}$ (26%) and 33 ng·day/mL (43%), respectively, based on population pharmacokinetic analysis. Accumulation of fam-trastuzumab deruxtecan-nxki was approximately 39% at steady-state (Cycle 3).

Distribution

Based on population pharmacokinetic analysis, the estimated volume of distribution of the central compartment (V_c) of fam-trastuzumab deruxtecan-nxki was 2.68 L.

For humans, DXd plasma protein binding is approximately 97% and the blood-to-plasma ratio is approximately 0.6, in vitro.

Elimination

The median elimination half-life ($t_{1/2}$) of fam-trastuzumab deruxtecan-nxki in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-5.7 days. Based on population pharmacokinetic analysis, the estimated systemic clearance of fam-trastuzumab deruxtecan-nxki was 0.41 L/day.

The median apparent elimination half-life ($t_{1/2}$) of DXd in patients with HER2-positive metastatic breast cancer, HER2-mutant NSCLC, and HER2-positive gastric cancer was approximately 5.4-6.1 days. Based on population pharmacokinetic analysis, the estimated apparent systemic clearance of DXd was 18.3 L/h.

Metabolism

The humanized HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro, DXd is primarily metabolized by CYP3A4.

Specific Populations

No clinically significant differences in the pharmacokinetics of fam-trastuzumab deruxtecan-nxki or DXd were observed for age (20-96 years); race (Asian [n=906] vs Non-Asian [n=763]), including White [n=619], Black or African American [n=36], and Other [n=108]; sex; body weight (27.3-125.4 kg); mild (total bilirubin $\leq$ ULN and any AST $>$ ULN or total bilirubin $>$ 1 to

1.5 times ULN and any AST, n=575) hepatic impairment; mild (creatinine clearance [CLcr] ≥ 60 and < 90 mL/min, n=646) or moderate (CLcr ≥ 30 and < 60 mL/min, n=251) renal impairment based on population pharmacokinetic analysis.

The pharmacokinetics of fam-trastuzumab deruxtecan-nxki or DXd in patients with moderate to severe hepatic impairment (total bilirubin > 1.5 ULN with any AST) or severe renal impairment (CLcr < 30 mL/min) is unknown.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A Inhibitors on DXd: Coadministration of itraconazole, a strong CYP3A inhibitor, with multiple doses of ENHERTU increased steady state AUC_{0-17 days} of fam-trastuzumab deruxtecan-nxki by 11% and DXd by 18%. The impact of these changes is not clinically meaningful.

Effect of OATP Inhibitors on DXd: Coadministration of ritonavir, a dual inhibitor of OATP1B/CYP3A, with multiple doses of ENHERTU increased steady state AUC_{0-17 days} of fam-trastuzumab deruxtecan-nxki by 19% and DXd by 22%. The impact of these changes is not clinically meaningful.

In Vitro Studies

Effects of DXd on CYP Enzymes: DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A nor induce CYP1A2, CYP2B6, or CYP3A.

Effects of DXd on Transporters: At clinically relevant concentrations (steady-state C_{max} of ~ 0.2 $\mu\text{mol/L}$), DXd has a low potential to inhibit OAT1 (IC₅₀ value of 12.7 $\mu\text{mol/L}$), OAT3, OCT1, OCT2, OATP1B1 (IC₅₀ value of 14.4 $\mu\text{mol/L}$), OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

Effects of Other Drugs on DXd: DXd is a substrate of OATP1B1, OATP1B3, MATE2-K, P-gp, MRP1, and BCRP.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ENHERTU or of other anti-HER2 products.

During the median 14-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast03 with a median ADA sampling period of 13 months, treatment-emergent ADA (or anti-fam-trastuzumab deruxtecan-nxki antibodies) developed in 1.6% (4/256) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0.4% (1/256).

During the median 7-month treatment period in HER2-positive breast cancer patients in DESTINY-Breast01 with a median ADA sampling period of 9 months, treatment-emergent ADA developed in 1.2% (3/249) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

During the median 8-month treatment period in HER2-low breast cancer patients in DESTINY-Breast04 with a median ADA sampling period of 8 months, treatment-emergent ADA developed in 2.0% (7/357) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/357).

During the median 3.5-month treatment period in HER2-mutant NSCLC patients in DESTINY-Lung02 with median ADA sampling period of 2.2 months, treatment-emergent ADA developed in 0.7% (1/143) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/249).

During the median 4.6-month treatment period in HER2-positive gastric or GEJ adenocarcinoma patients in DESTINY-Gastric01 with a median ADA sampling period of 4.6 months, treatment-emergent ADA developed in 7.3% (9/123) of patients who received ENHERTU. The incidence of treatment-emergent neutralizing antibodies against fam-trastuzumab deruxtecan-nxki was 0% (0/123).

Due to the limited number of patients who tested positive for ADA, the effect of treatment-emergent ADAs and treatment-emergent neutralizing antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of fam-trastuzumab deruxtecan-nxki is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fam-trastuzumab deruxtecan-nxki.

The topoisomerase inhibitor component of fam-trastuzumab deruxtecan-nxki, DXd, was clastogenic in both an in vivo rat bone marrow micronucleus assay and an in vitro Chinese hamster lung chromosome aberration assay and was not mutagenic in an in vitro bacterial reverse mutation assay.

Fertility studies have not been conducted with fam-trastuzumab deruxtecan-nxki. In a six-week repeat-dose toxicity study in rats, intravenous administration of fam-trastuzumab deruxtecan-nxki resulted in spermatid retention at 20 mg/kg and 60 mg/kg (approximately 4 and 9 times the human recommended dose of 5.4 mg/kg based on AUC, respectively). Decreased testes and epididymides weights, tubular atrophy/degeneration in testes, and reduced sperm count in epididymides were observed at a dose of 197 mg/kg (19 times the human recommended dose of 5.4 mg/kg based on AUC). In a three-month repeat-dose toxicity study in monkeys, intravenous administration of fam-trastuzumab deruxtecan-nxki resulted in decreased numbers of round spermatids in the testes at seminiferous tubule stages V to VI at ≥ 30 mg/kg (≥ 7 times the human recommended dose of 5.4 mg/kg based on AUC). Evidence of reversibility was observed in monkeys by the end of a three-month recovery period.

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

The efficacy of ENHERTU was evaluated in study DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive. Patients were excluded for a history of ILD/pneumonitis requiring treatment with steroids, ILD/pneumonitis at screening, or clinically significant cardiac disease. Patients were also excluded for untreated and symptomatic brain metastases, ECOG performance status >1 , or prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting.

Patients were randomized 1:1 to receive either ENHERTU 5.4 mg/kg (N=261) or ado-trastuzumab emtansine 3.6 mg/kg (N=263) by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and visceral versus non-visceral disease. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for all patients at baseline. The major efficacy outcomes were progression-free survival (PFS) as assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and overall survival (OS). Confirmed objective response rate (ORR) was an additional outcome measure.

The median age was 54 years (range: 20-83); 80% were <65 years and 99.6% were female. The majority of patients were Asian (60%), White (27%) and Black (3.6%). Eleven percent (11%) of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (63%) or 1 (37%) at baseline. Seventy-three percent had visceral disease, 16% had brain metastases at baseline, 52% were hormone receptor positive (HR+) and 48% of patients had received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 10%.

Efficacy results are summarized in Table 13 and Figure 1. At the time of the PFS analysis, 16% of patients had died and overall survival (OS) was immature.

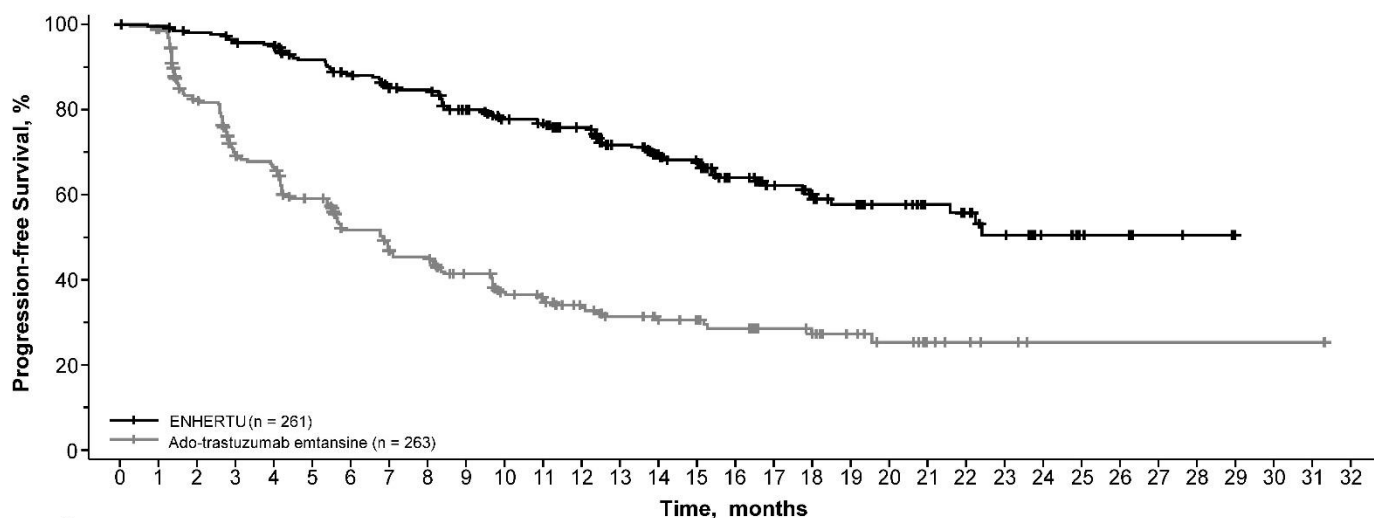
Table 13: Efficacy Results in DESTINY-Breast03

Efficacy Parameter	ENHERTU 5.4 mg/kg	Ado-trastuzumab emtansine 3.6 mg/kg
Progression-Free Survival (PFS) per BICR		
N	261	263
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value	p< 0.0001	
Confirmed Objective Response Rate (ORR) per BICR*		
N	248	241
n (%)	205 (82.7)	87 (36.1)
95% CI	(77.4, 87.2)	(30.0, 42.5)
Complete Response n (%)	39 (15.7)	20 (8.3)
Partial Response n (%)	166 (66.9)	67 (27.8)

CI = confidence interval; NR = not reached; NE=not estimable

*Analysis was performed based on the patients with measurable disease assessed by BICR at baseline.

**Figure 1: Kaplan-Meier Plot of Progression-Free Survival per BICR
(Intent-to-Treat Analysis Set)**



Number at Risk:

ENHERTU (261) 261 256 250 244 240 224 214 202 200 183 168 164 150 132 112 105 79 64 53 45 36 29 25 19 10 6 5 3 2 0

Ado-trastuzumab emtansine (263) 263 252 200 163 155 132 108 96 93 78 65 60 51 43 37 34 29 23 21 16 12 8 6 4 1 1 1 1 1 1 1 0

DESTINY-Breast01

The efficacy of ENHERTU was evaluated in study DESTINY-Breast01 (NCT03248492), a multicenter, single-arm, trial that enrolled 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status >1. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with brain metastases at baseline. The major efficacy outcomes were confirmed objective response rate (ORR) assessed by independent central review (ICR) using RECIST v1.1 and duration of response (DOR).

The median age was 55 years (range: 28-96); 76% of patients were <65 years. All 184 patients were female, and the majority were White (55%) or Asian (38%). Patients had an ECOG performance status of 0 (55%) or 1 (44%) at baseline. Ninety-two percent had visceral disease, 29% had bone metastases, and 13% had brain metastases. Fifty-three percent were HR+. Sum of diameters of target lesions were <5 cm in 42%, and ≥5 cm in 50% (not evaluable by central review in 8% of patients).

The median number of prior cancer regimens in the locally advanced/metastatic setting was 5 (range: 2-17). All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab.

Efficacy results are summarized in Table 14.

Table 14: Efficacy Results by Independent Central Review in DESTINY-Breast01

Efficacy Parameter	DESTINY-Breast01 N=184
Confirmed Objective Response Rate (95% CI)	60.3% (52.9, 67.4)
Complete Response	4.3%
Partial Response	56.0%
Duration of Response* Median, months (95% CI)†	14.8 (13.8, 16.9)

ORR 95% CI calculated using Clopper-Pearson method

*DOR is based on median duration of follow-up of 11.1 months.

†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

14.2 HER2-Low Metastatic Breast Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Breast04 (NCT03734029), a randomized, multicenter, open-label study that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+/ISH-, as determined at a central laboratory. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Patients were randomized 2:1 to receive either ENHERTU 5.4 mg/kg (N=373) by intravenous infusion every 3 weeks or physician's choice of chemotherapy (N=184, eribulin, capecitabine, gemcitabine, nab paclitaxel, or paclitaxel). Randomization was stratified by HER2 IHC status of tumor samples (IHC 1+ or IHC 2+/ISH-), number of prior lines of chemotherapy in the metastatic setting (1 or 2), and HR status/prior CDK4/6i treatment (HR+ with prior CDK4/6 inhibitor treatment, HR+ without prior CDK4/6 inhibitor treatment, or HR-). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for untreated or symptomatic brain metastases or ECOG performance status >1.

The major efficacy outcome measure was PFS in patients with HR+ breast cancer assessed by BICR based on RECIST v1.1. Additional efficacy outcome measures were PFS assessed by BICR based on RECIST v1.1 in the overall population (all randomized HR+ and HR- patients), OS in HR+ patients, and OS in the overall population.

The median age was 57 years (range: 28 to 81); 24% were age 65 or older; 99.6% were female; 48% were White, 40% were Asian, and 2% were Black or African American; 3.8% of patients were of Hispanic/Latino ethnicity. Patients had an ECOG performance status of 0 (55%) or 1 (45%) at baseline; 58% were IHC 1+, 42% were IHC 2+/ISH-; 70% had liver metastases, 33% had lung metastases, and 6% had brain metastases. In the metastatic setting, patients had a median of 3 prior lines of systemic therapy (range: 1 to 9) with 58% having 1 and 41% having 2 prior chemotherapy regimens; 3.9% were early progressors (progression in the neo/adjuvant setting). In HR+ patients, the median number of prior lines of endocrine therapy was 2 (range: 0 to 9) and 70% had prior CDK4/6i treatment.

Efficacy results are summarized in Table 15 and Figures 2 and 3.

Table 15: Efficacy Results in DESTINY-Breast04

Efficacy Parameter	HR+ Cohort		Overall Population (HR+ and HR- Cohorts)	
	ENHERTU (N=331)	Chemotherapy (N=163)	ENHERTU (N=373)	Chemotherapy (N=184)
Overall Survival				
Number of events (%)	126 (38.1)	73 (44.8)	149 (39.9)	90 (48.9)
Median, months (95% CI)	23.9 (20.8, 24.8)	17.5 (15.2, 22.4)	23.4 (20.0, 24.8)	16.8 (14.5, 20.0)
Hazard ratio (95% CI)	0.64 (0.48, 0.86)		0.64 (0.49, 0.84)	
p-value	0.0028		0.001	
Progression-Free Survival per BICR				
Number of events (%)	211 (63.7)	110 (67.5)	243 (65.1)	127 (69.0)
Median, months (95% CI)	10.1 (9.5, 11.5)	5.4 (4.4, 7.1)	9.9 (9.0, 11.3)	5.1 (4.2, 6.8)
Hazard ratio (95% CI)	0.51 (0.40, 0.64)		0.50 (0.40, 0.63)	
p-value	<0.0001		<0.0001	
Confirmed Objective Response Rate per BICR				
n (%)	175 (52.9)	27 (16.6)	195 (52.3)	30 (16.3)
95% CI	47.3, 58.4	11.2, 23.2	47.1, 57.4	11.3, 22.5
Complete Response n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)
Partial Response n (%)	164 (49.5)	26 (16.0)	183 (49.1)	28 (15.2)
Duration of Response per BICR				
Median, months (95% CI)	10.7 (8.5, 13.7)	6.8 (6.5, 9.9)	10.7 (8.5, 13.2)	6.8 (6.0, 9.9)

CI = confidence interval

Figure 2: Kaplan-Meier Plot of Overall Survival (Overall Population)

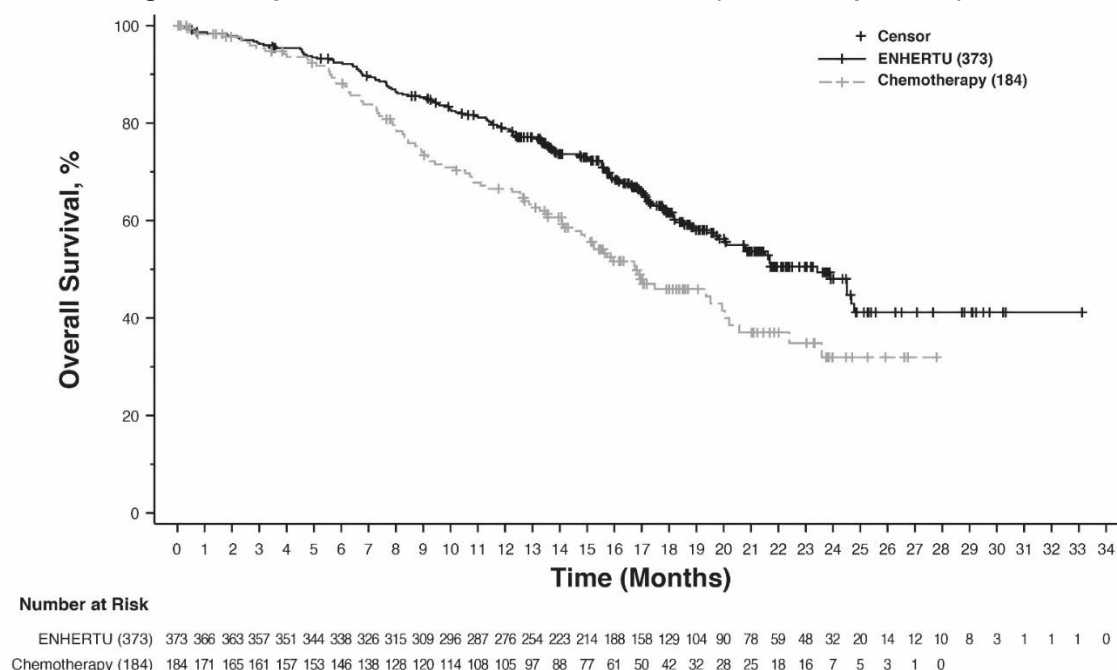
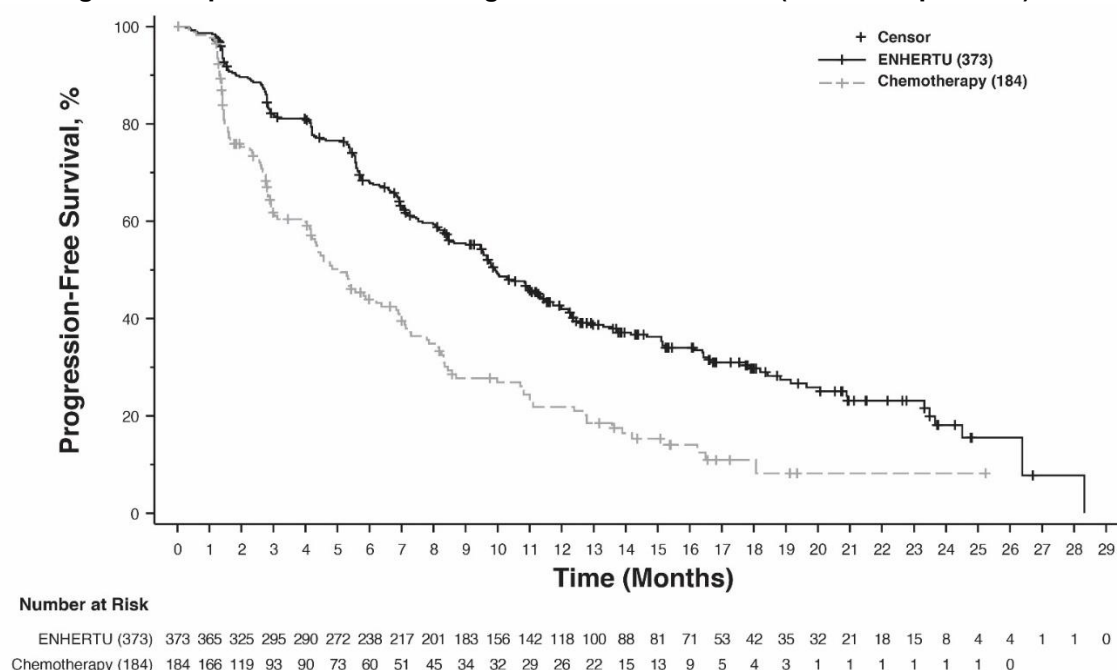


Figure 3: Kaplan-Meier Plot of Progression-Free Survival (Overall Population)



14.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU was evaluated in DESTINY-Lung01 (NCT03505710) and at two dose levels in DESTINY-Lung02 (NCT04644237). Patients were prospectively selected for treatment with ENHERTU based on the presence of activating HER2 (ERBB2) mutations by local testing using tissue. Samples from DESTINY-Lung01 were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation, Tissue-test) and Guardant360® CDx test (Guardant Health Inc., Plasma test). Demographic and baseline disease characteristics were similar for patients in DESTINY-Lung01 and DESTINY-Lung02, except for race (34% Asian vs 79% Asian, respectively). Response rates were consistent across dose levels. Increased rates of ILD/pneumonitis were observed at the higher dose. The approved recommended dose of 5.4 mg/kg intravenously every 3 weeks in the DESTINY-Lung02 study is described below [see *Adverse Reactions* (6.1)].

The efficacy of ENHERTU was evaluated in DESTINY-Lung02, a multicenter, multi-cohort, randomized, blinded, dose-optimization trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded. Patients received ENHERTU 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor imaging was obtained every 6 weeks and CT/MRI of the brain was mandatory for patients with stable brain metastases at baseline.

Results from an interim efficacy analysis in a pre-specified patient cohort are described below. The major efficacy outcomes were confirmed ORR as assessed by BICR using RECIST v1.1 and DOR.

The median age was 58 years (range 30 to 78); 69% were female; 79% were Asian, 12% were White, and 10% were other races; 29% had an ECOG performance status of 0 and 71% had 1; 33% had stable brain metastases; 94% had a mutation in the ERBB2 kinase domain and 6% had a mutation in the extracellular domain. The median number of prior regimens was 2 (range: 1 to 12); 100% of patients received prior platinum therapy, 71% received prior immunotherapy, and 44% received both in combination. Fifty percent of patients were never-smokers and 50% were former smokers; 96% of patients had adenocarcinoma histology.

Efficacy results are provided in Table 16.

Table 16: Efficacy Results for DESTINY-Lung02*

Efficacy Parameter	DESTINY-Lung02 N=52
Confirmed Objective Response Rate (95% CI)	57.7% (43.2, 71.3)
Complete Response	1.9%
Partial Response	55.8%
Duration of Response Median, months (95% CI)†	8.7 (7.1, NE)

ORR 95% CI calculated using Clopper-Pearson method

NE=not estimable

*Data cut-off: 22 June 2022

†Median DOR based on Kaplan-Meier estimate; 95% CI calculated using Brookmeyer-Crowley method

14.4 Locally Advanced or Metastatic Gastric Cancer

The efficacy of ENHERTU was evaluated in study DESTINY-Gastric01 (NCT03329690), a multicenter, open-label, randomized trial conducted in Japan and South Korea that enrolled 188 adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH positive), locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. HER2 expression was determined by a central lab on tissue obtained either before or after prior trastuzumab treatment. Patients were excluded for a history of treated or current ILD, a history of clinically significant cardiac disease, active brain metastases, or ECOG performance status >1.

Patients were randomized 2:1 to receive ENHERTU (N=126) 6.4 mg/kg intravenously every 3 weeks or physician's choice of chemotherapy: irinotecan monotherapy (N=55) 150 mg/m² intravenously every 2 weeks or paclitaxel monotherapy (N=7) 80 mg/m² intravenously weekly. Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH+), ECOG performance status (0 or 1), and region (Japan or South Korea). Tumor imaging assessments were performed at screening and every 6 weeks from the first treatment dose. Treatment was administered until unacceptable toxicity or disease progression. The major efficacy outcomes were ORR assessed by ICR according to RECIST v1.1 and OS in the intent-to-treat population. Additional efficacy outcomes were PFS and DOR.

The median age was 66 years (range 28 to 82); 76% were male; and 100% were Asian. All patients received a trastuzumab product. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; 45% had three or more prior regimens in the locally advanced or metastatic setting. A total of 30% of patients were identified as HER2-positive using tissue obtained following prior treatment with a trastuzumab product.

Efficacy results are summarized in Table 17, and the Kaplan-Meier curve for OS is shown in Figure 4.

Table 17: Efficacy Results in DESTINY-Gastric01

Efficacy Parameter	ENHERTU N=126	Irinotecan or Paclitaxel N=62
Overall Survival (OS)*		
Median, months (95% CI)†	12.5 (9.6, 14.3)	8.4 (6.9, 10.7)
Hazard ratio (95% CI)‡	0.59 (0.39, 0.88)	
p-value*	0.0097	
Progression-Free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Confirmed Objective Response Rate (ORR)§		
n (%)	51 (40.5)	7 (11.3)
95% CI¶	(31.8, 49.6)	(4.7, 21.9)
p-value#	<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Duration of Response (DOR)§		
Median, months (95% CI)†	11.3 (5.6, NR)	3.9 (3.0, 4.9)

CI = confidence interval; NR = not reached

*OS was evaluated following a statistically significant outcome of ORR.

†Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method

‡Based on the stratified Cox proportional hazards regression model (stratified by region)

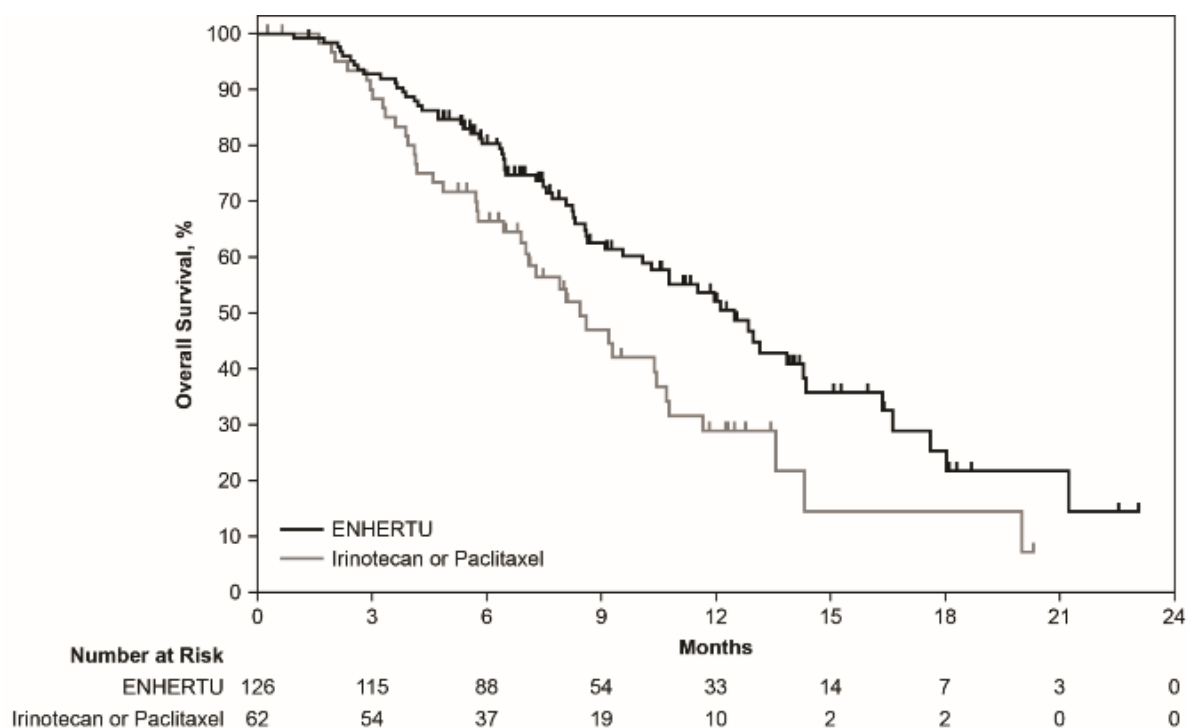
§Based on the stratified log-rank test (stratified by region)

¶Assessed by independent central review

¶95% exact binomial confidence interval

#Based on the stratified Cochran-Mantel-Haenszel test (stratified by region)

Figure 4: Kaplan-Meier Plot of Overall Survival



15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection is a white to yellowish white lyophilized powder supplied as:

Carton Contents	NDC
One 100 mg single-dose vial	NDC 65597-406-01

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution. Do not freeze. Do not shake the reconstituted or diluted solution [see *Dosage and Administration* (2.4)].

16.2 Special Handling

ENHERTU (fam-trastuzumab deruxtecan-nxki) is a hazardous drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Interstitial Lung Disease

- Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see *Warnings and Precautions* (5.1)].

Neutropenia

- Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see *Warnings and Precautions* (5.2)].

Left Ventricular Dysfunction

- Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see *Warnings and Precautions* (5.3)].

Embryo-Fetal Toxicity

- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1)].
- Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose [see *Use in Specific Populations* (8.3)].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose [see *Use in Specific Populations* (8.3)].

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see *Use in Specific Populations* (8.2)].

Infertility

- Advise males of reproductive potential that ENHERTU may impair fertility [see *Use in Specific Populations* (8.3)].

Manufactured by:
Daiichi Sankyo, Inc., Basking Ridge, NJ 07920

U.S. License No. 2128

Marketed by:
Daiichi Sankyo, Inc., Basking Ridge, NJ 07920 and AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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USPI-ENH-C9-0822-r005

Medication Guide

ENHERTU® (en-HER-too)
(fam-trastuzumab deruxtecan-nxki) for injection

What is the most important information I should know about ENHERTU?

ENHERTU can cause serious side effects, including:

- **Lung problems that may be severe, life-threatening or that may lead to death.** If you develop lung problems your healthcare provider may treat you with corticosteroid medicines. Tell your healthcare provider right away if you get any of the following signs and symptoms:
 - cough
 - trouble breathing or shortness of breath
 - fever
 - other new or worsening breathing symptoms (e.g., chest tightness, wheezing)
- **Low white blood cell count (neutropenia).** Low white blood cell counts are common with ENHERTU and can sometimes be severe. Your healthcare provider will check your white blood cell counts before starting ENHERTU and before starting each dose. Tell your healthcare provider right away if you develop any signs or symptoms of an infection or have fever or chills during treatment with ENHERTU.
- **Heart problems that may affect your heart's ability to pump blood.** Your healthcare provider will check your heart function before starting treatment with ENHERTU. Tell your healthcare provider right away if you get any of the following signs and symptoms:
 - new or worsening shortness of breath
 - coughing
 - feeling tired
 - swelling of your ankles or legs
 - irregular heartbeat
 - sudden weight gain
 - dizziness or feeling light-headed
 - loss of consciousness

Your healthcare provider will check you for these side effects during your treatment with ENHERTU. Your healthcare provider may reduce your dose, delay treatment or completely stop treatment with ENHERTU if you have severe side effects.

- **Harm to your unborn baby.** Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ENHERTU.
 - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with ENHERTU.
 - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for 7 months after the last dose.
 - **Males** who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with ENHERTU and for 4 months after the last dose.

See **“What are the possible side effects of ENHERTU?”** for more information about side effects.

What is ENHERTU?

ENHERTU is a prescription medicine used to treat adults who have:

- human epidermal growth factor receptor 2 (HER2)-positive breast cancer that cannot be removed by surgery or that has spread to other parts of the body (metastatic), and who have received a prior anti-HER2 breast cancer treatment:
 - for metastatic disease, **or**
 - have breast cancer that has come back during or within 6 months of completing treatment for their early-stage breast cancer.
- HER2-low breast cancer that cannot be removed by surgery or that has spread to other parts of your body (metastatic), and who have received a prior chemotherapy
 - for metastatic disease, **or**
 - your disease has returned during or within 6 months of completing adjuvant chemotherapy (after surgery). Your healthcare provider will perform a test to make sure ENHERTU is right for you.
- non-small cell lung cancer (NSCLC) that has a certain mutation in the HER2 gene and cannot be removed by surgery or has spread to other parts of your body (metastatic), and who have received a prior treatment. Your healthcare provider will perform a test to make sure ENHERTU is right for you.
- stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that is HER2-positive and has spread to areas near your stomach (locally advanced) or that has spread to other parts of your body (metastatic), and who have received a prior trastuzumab-based regimen.

It is not known if ENHERTU is safe and effective in children.

Before you receive ENHERTU, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems.
- have signs or symptoms of an infection.
- have or have had any heart problems.

- are breastfeeding or plan to breastfeed. It is not known if ENHERTU passes into your breast milk. Do not breastfeed during treatment with ENHERTU and for 7 months after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ENHERTU?

- You will receive ENHERTU into your vein through an intravenous (IV) line by your healthcare provider.
- ENHERTU is given 1 time every three weeks (21-day treatment cycle).
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will give you medicines before your infusion to help prevent nausea and vomiting.
- Your healthcare provider may slow down or temporarily stop your infusion of ENHERTU if you have an infusion-related reaction, or permanently stop ENHERTU if you have severe infusion reactions.
- If you miss a planned dose of ENHERTU, call your healthcare provider right away to schedule an appointment. Do not wait until the next planned treatment cycle.

What are the possible side effects of ENHERTU?

ENHERTU can cause serious side effects. See "What is the most important information I should know about ENHERTU?"

The most common side effects of ENHERTU, when used in people with metastatic breast cancer and HER2-mutant non-small cell lung cancer include:

- | | |
|----------------------------------|---------------------------------|
| • nausea | • constipation |
| • low white blood cell counts | • muscle or bone pain |
| • low red blood cell counts | • decreased appetite |
| • feeling tired | • low levels of blood potassium |
| • low platelet counts | • diarrhea |
| • increased liver function tests | • cough |
| • vomiting | |
| • hair loss | |

The most common side effects of ENHERTU, when used in people with HER2-positive gastric or GEJ adenocarcinoma, include:

- | | |
|----------------------------------|---------------------------------|
| • low red blood cell counts | • diarrhea |
| • low white blood cell counts | • low levels of blood potassium |
| • low platelet counts | • vomiting |
| • nausea | • constipation |
| • decreased appetite | • fever |
| • increased liver function tests | • hair loss |
| • feeling tired | |

ENHERTU may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ENHERTU. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ENHERTU.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ENHERTU that is written for healthcare professionals.

What are the ingredients in ENHERTU?

Active Ingredient: fam-trastuzumab deruxtecan-nxki.

Inactive Ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

Manufactured by: Daiichi Sankyo, Inc., Basking Ridge, NJ 07920

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USMG-ENH-C9-0822-r005

For more information, call 1-877-437-7763 or go to <https://www.ENHERTU.com>.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 08/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761139Orig1s021

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Enhertu® (fam-trastuzumab deruxtecan-nxki)

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	sBLA (supplemental BLA)
Application Number	761139 (S-21)
Priority or Standard	Priority
Submit Date	1/18/2022, 2/16/2022
Received Date	1/18/2022, 2/16/2022
PDUFA Goal Date	8/16/2022
Division/Office	Division of Oncology 2 / Office of Oncologic Drugs
Review Completion Date	<i>Electronic stamp date</i>
Established Name	fam-trastuzumab deruxtecan-nxki
(Proposed) Trade Name	ENHERTU
Pharmacologic Class	Antibody-drug conjugate
Code name	
Applicant	Daiichi Sankyo, Inc.
Formulation(s)	For injection: 100 mg of fam-trastuzumab deruxtecan-nxki as a white to yellowish white lyophilized powder in a single-dose vial for reconstitution and further dilution
Dosing Regimen	5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Enhertu[®] (fam-trastuzumab deruxtecan-nxki)

Applicant Proposed Indication(s)/Population(s)	Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

GLOSSARY

AC	adjudication committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
BC	breast cancer
BLA	Biologics License Application
BTR	best tumor response
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Event
CYP	cytochrome
DCO	data cut-off
DCR	disease control rate
DoR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
ER	exposure-response
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	gastric cancer
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2

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ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central review
IHC	immunohistochemistry
ILD	interstitial lung disease
IV	intravenous
LV	left ventricular
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NDA	new drug application
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PopPK	population pharmacokinetics
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QTL	quality tolerance limit
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event

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sBLA supplemental Biologic License Application

SoD sum of diameter

T-DXd trastuzumab deruxtecan

TEAE treatment emergent adverse event

U.S. United States

USPI United States Prescribing Information

Enhertu® (fam-trastuzumab deruxtecan-nxki)

1 EXECUTIVE SUMMARY

1.1 PRODUCT INTRODUCTION

Enhertu (fam-trastuzumab deruxtecan-nxki [T-DXd]) is a HER2-directed antibody and topoisomerase inhibitor conjugate that is administered as an intravenous infusion. The anti-HER2 component, MAAL-9001, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb). The released drug, MAAA-1181a, is a topoisomerase I inhibitor derivative of exatecan. The mAb is covalently conjugated to a drug-linker, MAAA1162a, that is composed of a cleavable maleimide tetrapeptide linker and the released drug.

T-DXd is approved 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.
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

The recommended indication for accelerated approval is:

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.

The recommended dosage regimen for the proposed indication is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity, administered over 90 minutes for the first cycle and over 30 min in subsequent cycles if prior infusions were well tolerated.

1.2 CONCLUSIONS ON THE SUBSTANTIAL EVIDENCE OF EFFECTIVENESS

Daiichi Sankyo has provided substantial evidence of effectiveness supporting the accelerated approval of T-DXd under 21 CFR part 314 subpart H, for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

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The recommendation for accelerated approval of T-DXd is supported by the results of Study DS8201-A-U206 (Study U206; DESTINY-Lung02) and Study DS8201-A-U204 (Study U204; DESTINY-Lung01). Study U206 is an ongoing, international, multi-center, randomized, dose-optimization trial comparing T-DXd 5.4 mg/kg and 6.4 mg/kg by intravenous infusion every 3 weeks. The trial enrolled 102 patients with HER2-mutated NSCLC at the 5.4 mg/kg dose level and 50 patients at the 6.4 mg/kg dose level. Study U204 (Cohort 2) was an international, multi-center, single-arm trial that enrolled 91 patients with NSCLC with *HER2* (*ERBB2*) mutations and had received prior systemic therapy. Patients received T-DXd 6.4 mg/kg by intravenous infusion every 3 weeks. The primary endpoint of both Study U206 and Study U204 was overall response rate (ORR) by blinded independent central review (BICR). The primary efficacy population to support this application was the cohort of patients in Study U206 treated with T-DXd 5.4 mg/kg with at least 4.5 months follow-up as of the March 24, 2022, data cutoff (DCO) date. The ORR in this cohort of patients treated with T-DXd 5.4 mg/kg was **58% (95% CI: 43, 71) with a median duration of response (DOR) of 8.7 months (95% confidence interval [CI]: 7.1, not estimable [NE])**, based on 90 additional days of follow-up and a DCO date of June 22, 2022. This ORR was consistent with response rates observed at the higher dose level, T-DXd 6.4 mg/kg, in Study U204 and Study U206 (43-55%).

Although no new safety signals were identified during the course of this review, interstitial lung disease (ILD) and pneumonitis, which were evaluated by a blinded ILD adjudication committee, were more frequent in the cohorts of patients treated at the 6.4 mg/kg dose level. In Study U206, the incidence of ILD/pneumonitis was 14% among 50 patients treated at the 6.4 mg/kg dose level compared to 6% among 101 patients treated at the 5.4 mg/kg dose level. Based on consistent efficacy and reduced toxicity with the lower dose compared to the higher dose, the FDA review teams recommended a treatment dose of T-DXd 5.4 mg/kg administered every 3 weeks.

The submitted evidence meets the statutory evidentiary standard for accelerated approval based on an ORR of sufficient magnitude and duration that is reasonably likely to predict clinical benefit in patients with *HER2*-mutated NSCLC. The lower bound of the 95% confidence interval around the point estimate for ORR observed in the primary efficacy population from Study U206 is greater than the point estimate for ORR observed with FDA-approved available therapies for this refractory population (e.g., docetaxel, docetaxel in combination with ramucirumab).

This is the first approval for patients with *HER2*-mutant NSCLC who have received prior systemic therapy. In the context of its safety profile, the ORR and durable responses observed with T-DXd 5.4 mg/kg administered every 3 weeks are reasonably likely to predict clinical benefit and provide a meaningful advantage over available treatments for this disease.

1.3 BENEFIT-RISK ASSESSMENT (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer deaths worldwide and in the U.S., accounting for almost a quarter of cancer-related mortality in the U.S. in 2021 (Siegel 2021). Population-level mortality from NSCLC has declined over the past 10 years, with improvements in survival likely related to the identification of oncogenic driver mutations and other genomic alterations, such as in *EGFR* and *ALK*, and the development and approval of therapies targeting these alterations (Howlader 2020). Despite these advances, metastatic NSCLC remains a fatal, incurable disease with a 5-year survival rate of <10%.

HER2 (also known as *Erb-B2 receptor tyrosine kinase 2 [ERBB2]*) mutations occur in approximately 1.6% of all NSCLC (Mazieres, 2013). The majority of these mutations are activating mutations involving Exon 20 of the *HER2 (ERBB2)* gene. Patients with *HER2*-mutated NSCLC tend to be female, never smokers, and have a median age around 60 years. Median survival in patients with metastatic *HER2*-mutated NSCLC is 1.4 to 2.1 years (Pillai, 2017). Available treatment options for patients who have disease progression following initial systemic therapy in the metastatic setting include ramucirumab plus docetaxel, single agent chemotherapy, or an anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve. In the REVEL study, ramucirumab plus docetaxel was found to have an ORR of 23% (95% CI: 20, 26), however its use has been limited by toxicity (Garon, 2014).

T-DXd is an antibody-topoisomerase inhibitor conjugate that targets *HER2*. T-DXd is currently approved for the treatment of patients with *HER2*-positive metastatic breast cancer (5.4 mg/kg every 3 weeks) and *HER2*-positive gastric cancer (6.4 mg/kg every 3 weeks). Support for this application is based on efficacy and safety data from Study U206 (DESTINY-Lung02) and Study U204 (DESTINY-Lung01). Study U206 was an international, multi-center randomized study, which included patients with unresectable or metastatic NSCLC with an activating *HER2 (ERBB2)* mutation who had received prior systemic therapy who were randomized (2:1) to either T-DXd 5.4 mg/kg every 3

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weeks (n=102) or T-DXd 6.4 mg/kg every 3 weeks (n=50) until disease progression or unacceptable toxicity. Study U204 was an international, multi-center single-arm study, which included 91 patients with unresectable or metastatic NSCLC with an activating *HER2* (*ERBB2*) mutation who had received prior systemic therapy treated with T-DXd 6.4 mg/kg every 3 weeks until disease progression or unacceptable toxicity. In both Study U206 and Study U204, the primary endpoint was ORR by BICR per RECIST 1.1 criteria. The adverse event of special interest, interstitial lung disease (ILD)/pneumonitis was evaluated by independent central review (i.e., an ILD adjudication committee).

The primary efficacy population consisted of 52 patients in an early prespecified interim analysis of the 5.4 mg/kg arm of Study U206 with at least 4.5 months follow-up as of the March 2022 data cutoff. This allowed for at least three imaging assessments in this cohort. All patients in the primary efficacy population received prior systemic therapy, including 73% who received prior a-PD-(L)1 therapy. The confirmed ORR by BICR in the primary efficacy population was 58% (95% CI: 43, 71) with a median DOR of 8.7 months (95% CI: 7.1, NE). This ORR was consistent with the response rates observed with T-DXd 6.4 mg in Study U204 and Study U206 (43-55%).

T-DXd has a manageable safety profile when assessed in the context of a life-threatening disease. The safety review focused on 102 patients in the 5.4 mg/kg arm in Study U206 (i.e., the primary safety population) and was supported by 50 patients in the 6.4 mg/kg arm, as well as 91 patients treated at the 6.4 mg/kg dose level in Study U204 and 11 patients treated at the 6.4 mg/kg dose level in the first-in-human trial, Study DS8201-A-J101 (Study J101). The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia. Permanent discontinuation of T-DXd due to adverse reactions occurred in 5% of patients and dose interruptions of T-DXd due to adverse reactions occurred in 23% of patients. T-DXd is also known to cause serious ILD/pneumonitis, which is currently addressed through a boxed warning in product labeling to advise health professionals of the risk. There was one death in the primary safety population in Study U206, which was due to ILD/pneumonitis. The rate of ILD/pneumonitis was 6% in the 5.4 mg/kg arm of Study U206 compared with 14% in the 6.4 mg/kg arm. The rate of ILD in Study U204 (6.4 mg/kg) was 26%. The

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lower rate of ILD/pneumonitis for patients treated at 5.4 mg/kg every 3 weeks compared to 6.4 mg/kg every 3 weeks suggest a dose-dependent reduction in toxicity with the lower dose.

Applications for Pre-Market Approval (PMA) for the Oncomine Dx Target Test (tumor tissue) and Guardant360 CDx (plasma) were submitted to the Center for Devices and Radiological Health (CDRH) for contemporaneous review and approval with this biologics license application (BLA).

This supplemental BLA represents a new treatment option for an indication with unmet medical need. The applicant used advice from the FDA Oncology Center of Excellence's Project Optimus to conduct a dose randomization study, which led to a lower dose being approved. The benefit-risk profile for this indication is favorable, with the results of Studies U204 and U206 providing substantial evidence of effectiveness in this setting. The magnitude of the ORR observed at the 5.4 mg/kg dose level in Study U206, supported by efficacy data at the 6.4 mg/kg dose level in Study U204 and Study U206, is likely to predict clinical benefit in patients with *HER2*-mutated NSCLC. (b) (4)

Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication:

*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.*

Due to the consistent efficacy results across dose levels and reduced toxicity observed at the 5.4 mg/kg dose level, the recommended dose is T-DXd 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Lung cancer is the leading cause of cancer deaths accounting for almost 25% of all cancer deaths in the U.S. in 2021 (Siegel, 2021). <i>HER2 (ERBB2)</i> mutations occur in 1.6% of NSCLC (Mazieres 2013). - Median survival in patients with metastatic NSCLC with <i>HER2 (ERBB2)</i> mutations is 1.4 to 2.1 years (Pillai, 2017).	Unresectable or metastatic NSCLC with a <i>HER2 (ERBB2)</i> mutation is a life-threatening disease with poor survival. Tumors with a <i>HER2 (ERBB2)</i> mutation represent a rare subset of NSCLC.
Current Treatment Options	- There are no currently FDA approved therapies specifically for the treatment of patients with NSCLC whose tumors harbor <i>HER2 (ERBB2)</i> mutations. Treatment options for patients with NSCLC whose tumors harbor <i>HER2 (ERBB2)</i> mutations who have progressed on prior systemic therapy are the same as those used for patients with NSCLC without a specific driver mutation, although the effectiveness of most of these treatments has not been specifically studied in this subpopulation. - For patients with progression of disease following initial systemic therapy, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with ORRs of 6-23% with median DORs in the range of 4-9 months, or single agent anti-PD-(L)1 antibodies if not received in the first-line setting, associated with ORRs of 14-20% and median DORs in the range of 16-17 months.	There is an unmet medical need for patients with previously treated NSCLC harboring <i>HER2 (ERBB2)</i> mutations whose disease has progressed on or after prior systemic therapy. This conclusion is based on the observed ORRs, DORs, and overall survival (OS) reported for therapies currently used in clinical practice for the treatment of this patient population.
Benefit	Study U206 was an international, multi-center randomized study, which included patients with unresectable or metastatic NSCLC with an activating <i>HER2 (ERBB2)</i> mutation who had received prior systemic therapy who were randomized (2:1) to either T-DXd 5.4 mg/kg every 3	The magnitude of the ORR observed at the 5.4 mg/kg dose level in Study U206 is likely to predict clinical benefit in patients with <i>HER2</i>-mutated NSCLC and meets the evidentiary standard for

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weeks (n=102) or T-DXd 6.4 mg/kg every 3 weeks (n=50) until disease progression or unacceptable toxicity. A prespecified interim analysis including 52 patients treated at the 5.4 mg/kg dose level with at least 4.5 months follow-up represented the primary efficacy population. - The confirmed ORR by BICR in the primary efficacy population was 58% (95% CI: 43, 71) with a median DOR of 8.7 months (95% CI: 7.1, NE). - The response rate at the 5.4 mg/kg dose level was consistent with the response rates observed with T-DXd 6.4 mg/kg in Study U204 and Study U206 (43-55%).	accelerated approval. The ORR in Study U206 and Study U204 was consistent across dose levels, supporting the benefit of treatment at the 5.4 mg/kg dose level in this population.
Risk and Risk Management	- The primary safety population supporting this sBLA included patients randomized to the 5.4 mg/kg dose level in Study U206. - Supportive data were submitted from the 6.4 mg/kg dose level in Study U206, Study U204, and Study J101. - The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia. - The rate of ILD/pneumonitis was 6% in the 5.4 mg/kg arm of Study U206 compared with 14% in the 6.4 mg/kg arm. The rate of ILD in Study U204 (6.4 mg/kg) was 26%.	The observed safety profile is acceptable in the context of the treatment of a life-threatening disease and is overall consistent with the known adverse effects of T-DXd. T-DXd is known to cause serious ILD/pneumonitis, which is currently addressed through a boxed warning in the product labeling. The rate of ILD/pneumonitis was lower in the 5.4 mg/kg dose cohort, supporting approval of this indication at a recommended dose of 5.4 mg/kg every 3 weeks.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There was one death in the primary safety population, which was due to ILD/pneumonitis. Permanent discontinuation of T-DXd due to adverse reactions occurred in 5% of patients and dose interruptions of T-DXd due to adverse reactions occurred in 23% of patients in the primary safety population.	

1.4 PATIENT EXPERIENCE DATA

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	

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☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

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2 THERAPEUTIC CONTEXT

2.1 ANALYSIS OF CONDITION

The Applicant's Position:

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in the world ([Sung et al. 2021](#)). In 2020, there were an estimated 2.21 million new cases of lung cancer globally (11.4% of all new cancers), with an estimated 1.8 million deaths due to the disease (18.0% of all cancer deaths; [Sung et al. 2021](#)). Despite progress in earlier detection, a majority of lung cancers (57% in the United States (U.S.) for the 2009 to 2015 period; [Howlader et al. 2019](#)) are still commonly diagnosed at the metastatic stage, when the disease is not curable, with a 5-year relative survival rate of 5.2% ([Howlader et al. 2019](#)).

The therapeutic approach to lung cancers is based on the specific histologic and genetic characteristics of the tumor. Lung cancers are classified into 2 major histologic types: the most common is non-small cell lung cancer (NSCLC), found in ~85% of all lung cancers; small-cell lung cancer occurs in ~15% of lung cancers ([Pikor et al. 2013](#)).

The identification of specific genomic alterations in tumors or immune biomarkers that are indicative of therapeutic efficacy of targeted therapies or immunotherapy transformed the therapeutic approach to and prognosis of metastatic NSCLC ([NCCN 2020](#)). Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer, with 5-year survival rates ranging from 15% to 50% depending on the predictive biomarker.

HER2 (human epidermal growth factor receptor 2; also known as Erb-B2 receptor tyrosine kinase 2 [ERBB2]) is an emerging targetable oncogenic driver in NSCLC. Sequencing of HER2 in lung tumors revealed the presence of somatic mutations within the kinase domain of HER2 in ~3% of all lung tumors (all of which were adenocarcinomas) ([The Cancer Genome Atlas Research Network 2014](#); [Pillai et al. 2017](#)), suggesting a potential role for HER2-targeted therapies in patients whose tumors contain HER2 mutations ([Stephens et al. 2004](#)). The majority of these mutations occur in exon 20 ([Pillai et al. 2017](#)). HER2 mutations and other driver oncogene genomic alterations are usually mutually exclusive ([Stephens et al. 2004](#); [Pao and Girard 2011](#); [Mazieres et al. 2013](#); [The Cancer Genome Atlas Research Network 2014](#); [Pillai et al. 2017](#)). Patients with tumors that have HER2 mutations tend to be female, never smoker, and younger (median age around 60 years) ([Pillai et al. 2017](#)).

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The FDA's Assessment:

FDA agrees with the Applicant's assessment of the condition. *HER2* (*ERBB2*) mutations have been reported in approximately 1.6% of cases of NSCLC, with the majority of these tumors demonstrating adenocarcinoma histology (Mazieres 2013). Median survival among patients with metastatic, *HER2*-mutant NSCLC is 1.4 to 2.1 years (Pillai, 2017).

2.2 ANALYSIS OF CURRENT TREATMENT OPTIONS

In the second-line metastatic setting, single agents docetaxel and pemetrexed are common chemotherapeutic options (Planchard et al. 2018; NCCN 2020). Another therapeutic option is the combination ramucirumab plus docetaxel (Garon et al. 2014), which was shown to improve overall survival (OS) and progression-free survival (PFS) over docetaxel monotherapy. For most previously treated patients with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitor-naïve NSCLC, the current standard of care irrespective of PD-L1 expression in this setting is the use of anti-PD1/PD-L1 agents (Planchard et al. 2018; Akamatsu et al. 2019; NCCN 2020).

There are currently no targeted therapies specifically approved for patients with metastatic *HER2*-mutant NSCLC. Efficacy of currently approved treatment options for patients without actionable oncogenic driver mutations in the second-line setting is limited, with objective response rates (ORRs) ranging from 5.8% to 22.9%, median PFS ranging from 2.8 months to 4.5 months, and median OS ranging from 6.0 months to 13.8 months (Applicant - Table). The current standard of care for patients with unresectable or metastatic *HER2*-mutant NSCLC who have received a prior systemic therapy is docetaxel with or without ramucirumab (Applicant - Table).

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Applicant - Table 1: Treatment Options in Second Line in the Metastatic Setting

Product Name	Relevant Indication ^a	Year and Type of Approval	Dosing Administration	Efficacy Information	Important Safety and Tolerability Issues
Docetaxel (TAXOTERE®: TAXOTERE PI 2020)	Single agent for locally advanced or metastatic NSCLC after platinum therapy failure	1999 (NSCLC) Regular approval	75 mg/m ² single agent Q3W as IV infusion over 1 hour	TAX317 (TAXOTERE PI 2020): <u>Docetaxel</u> : (n = 55) Median OS: 7.5 months (95% CI: 5.5, 12.8) (risk ratio: 0.56 [95% CI: 0.35, 0.88]; <i>P</i> value = 0.01) Time to progression: 12.3 weeks (95% CI: 9.0, 18.3) ORR: 5.5% (95% CI: 1.1, 15.1) <u>Best supportive care</u> : (n = 49) Median OS: 4.6 months (95% CI: 3.7, 6.1) Time to progression: 7.0 weeks (95% CI: 6.0, 9.3) ORR: not applicable	<u>Docetaxel</u> (TAXOTERE PI 2020): Second primary malignancies (AML, MDS, NHL, and renal cancer) Cutaneous reactions including erythema of the extremities with edema followed by desquamation and severe skin toxicity Neurologic reactions including paresthesia, dysesthesia, and pain Eye disorders (cystoid macular edema) Asthenia Embryo-fetal toxicity Alcohol content that may affect the CNS Tumor lysis syndrome Most common adverse reactions: infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.
Ramucirumab (CYRAMZA®: CYRAMZA PI 2020) plus docetaxel	Ramucirumab in combination with docetaxel for treatment of metastatic NSCLC with disease	2014 Regular approval	CYRAMZA 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel	REVEL (CYRAMZA PI 2020): <u>Ramucirumab + docetaxel</u> : (n = 628) Median OS: 10.5 months (95% CI: 9.5, 11.2) (HR: 0.86 [95% CI: 0.75, 0.98]; <i>P</i> value = 0.024)	<u>CYRAMZA</u> (CYRAMZA PI 2020): Hemorrhage including GI hemorrhage GI perforations Impaired wound healing Arterial thromboembolic events Hypertension

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Product Name	Relevant Indication ^a	Year and Type of Approval	Dosing Administration	Efficacy Information	Important Safety and Tolerability Issues
	progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.			Median PFS: 4.5 months (95% CI: 4.2, 5.4) (HR: 0.76 [95% CI: 0.68, 0.86]; <i>P</i> value <0.001) ORR: 22.9% (95% CI: 19.7, 26.4) (<i>P</i> value <0.001) <u>Docetaxel monotherapy:</u> (n = 625) Median OS: 9.1 months (95% CI: 8.4, 10.0) Median PFS: 3.0 months (95% CI: 2.8, 3.9) ORR: 13.6% (95% CI: 11.0, 16.5)	Infusion related reactions Worsening of preexisting hepatic impairment Posterior reversible encephalopathy syndrome Thyroid dysfunction Embryo-fetal toxicity Most common adverse reactions in patients treated with CYRAMZA plus docetaxel at a rate of ≥30% and ≥2% higher than placebo plus docetaxel: neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation
Nivolumab (OPDIVO®: OPDIVO PI 2020)	Patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on	2015 (NSCLC) Regular approval	240 mg Q2W or 480 mg Q4W as IV infusion over 30 min	CheckMate-057 (Borghaei et al. 2015): <u>Nivolumab:</u> (n = 135) Median OS: 9.2 months (95% CI: 7.3, 13.3) (HR: 0.59 [95% CI: 0.44, 0.79]; <i>P</i> value <0.001) Median PFS: 3.5 months (95% CI: 2.1, 4.9) (HR: 0.62 [95% CI: 0.47, 0.81]; <i>P</i> value <0.001) Confirmed ORR: 20% (95% CI: 14, 28) Median DoR: NR (range: 2.9 to 20.5+)^b	<u>Nivolumab (OPDIVO PI 2020; as single agent):</u> Immune-mediated pneumonitis Immune-mediated colitis Immune-mediated hepatitis Immune-mediated endocrinopathies (hypophysitis, adrenal insufficiency, changes in thyroid function, hyperglycemia) Immune-mediated nephritis and renal dysfunction Immune-mediated skin adverse reactions Immune-mediated encephalitis Infusion-related reactions

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Product Name	Relevant Indication ^a	Year and Type of Approval	Dosing Administration	Efficacy Information	Important Safety and Tolerability Issues
	FDA-approved therapy for these aberrations prior to receiving OPDIVO.			<u>Docetaxel</u> : (n = 137) Median OS: 6.0 months (95% CI: 5.1, 7.3) Median PFS: 2.8 months (95% CI: 2.1, 3.5) Confirmed ORR: 9% (95% CI: 5, 15) Median DoR: 8.4 months (range: 1.4+ to 15.2+) ^b	Complications of allogeneic HSCT Embryo-fetal toxicity Most common adverse reactions (incidence ≥20%): fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting
Pembrolizumab (KEYTRUDA®: KEYTRUDA PI 2020)	As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease	2015 Accelerated approval	200 mg Q3W or 400 mg Q6W as IV infusion over 30 min	KEYNOTE-010 (Herbst et al. 2016): <u>Pembrolizumab 2 mg/kg</u> : (n = 345) Median OS: 10.4 months (95% CI: 9.4, 11.9) (HR: 0.71 [95% CI: 0.58, 0.88]; <i>P</i> value = 0.0008) Median PFS: 3.9 months (95% CI: 3.1, 4.1) (HR: 0.88 [95% CI: 0.74, 1.05]; <i>P</i> value = 0.07) ORR: 18.0% (95% CI: 14.1, 22.5) Median DoR: NR (IQR: 4.2 to 10.5) <u>Pembrolizumab 10 mg/kg</u> : (n = 346) Median OS: 12.7 months (95% CI: 10.0, 17.3) (HR: 0.61 [95% CI: 0.49, 0.75]; <i>P</i> value <0.0001) Median PFS: 4.0 months (95% CI: 2.7, 4.3) (HR: 0.79 [95% CI: 0.66, 0.94]; <i>P</i> value = 0.004)	<u>Pembrolizumab</u> (KEYTRUDA PI 2020 ; as single agent): Immune-mediated adverse reactions including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection Infusion-related reactions Complications of allogeneic HSCT Embryo-fetal toxicity Most common adverse reactions (reported in ≥20% of patients): fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain

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Product Name	Relevant Indication ^a	Year and Type of Approval	Dosing Administration	Efficacy Information	Important Safety and Tolerability Issues
	progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.			ORR: 18.5% (95% CI: 14.5, 23.0) Median DoR: NR (IQR: 4.2 to 12.5) <u>Docetaxel</u>: (n = 343) Median OS: 8.5 months (95% CI: 7.5, 9.8) Median PFS: 4.0 months (95% CI: 3.1, 4.2) ORR: 9.3% (95% CI: 6.5, 12.9) Median DoR: 6 months (IQR: 2.7 to 6.1)	
Atezolizumab (TECENTRIQ®: TECENTRIQ PI 2020)	For the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved	2017 Regular approval	<u>As single agent</u>: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W <u>When administered with chemotherapy with or without bevacizumab</u>: 1200 mg Q3W prior to chemotherapy and bevacizumab <u>Following completion of 4-6 cycles of</u>	OAK (Rittmeyer et al. 2017): <u>Atezolizumab</u>: (n = 425) - Median OS: 13.8 months (95% CI: 11.8, 15.7) (HR: 0.73 [95% CI: 0.62, 0.87]; <i>P</i> value = 0.0003) - Median PFS: 2.8 months (95% CI: 2.6, 3.0) (HR: 0.95 [95% CI: 0.82, 1.10]; <i>P</i> value = 0.38) - ORR: 18% (95% CI not provided) - Median DoR: 16.0 months (95% CI: 9.7, NE) <u>Docetaxel</u>: (n = 425) - Median OS: 9.6 months (95% CI: 8.6, 11.2) - Median PFS: 4.0 months (95% CI: 3.3, 4.2) - ORR: 16% (95% CI not provided)	<u>Atezolizumab</u> (TECENTRIQ PI 2020; as single agent): Immune-mediated pneumonitis Immune-mediated hepatitis Immune-mediated colitis Immune-mediated endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus) Infections that can be severe or life-threatening Infusion-related reactions Embryo-fetal toxicity Most common adverse reactions (≥20%): fatigue/asthenia, nausea, cough, dyspnea, and decreased appetite

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Product Name	Relevant Indication ^a	Year and Type of Approval	Dosing Administration	Efficacy Information	Important Safety and Tolerability Issues
	therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.		<u>chemotherapy, and if bevacizumab is discontinued:</u> 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W	– Median DoR: 6.2 months (95% CI: 4.9, 9.2)	
Pemetrexed (ALIMTA®: ALIMTA PI 2019)	For locally advanced or metastatic non-squamous NSCLC after prior chemotherapy as a single agent	2004 Regular approval	500 mg/m ² IV on Day 1 of each 21-day cycle	Hanna et al. 2004: <u>Pemetrexed:</u> (n = 283) Median OS: 8.3 months (95% CI not reported) (HR: 0.99 [95% CI: 0.82, 1.2]; <i>P</i> value = 0.226) Median PFS: 2.9 months (range: 0 to 18.2) (HR: 0.97 [95% CI: 0.82, 1.16]; <i>P</i> value = 0.759) ORR: 9.1% Median DoR: 4.6 months (range: 2.1 to 15.3) <u>Docetaxel:</u> (n = 288) Median OS: 7.9 months (95% CI not reported) Median PFS: 2.9 months (range: 0 to 19.5) ORR: 8.8% Median DoR: 5.3 months (range: 1.7 to 11.7)	<u>Pemetrexed (ALIMTA PI 2019):</u> Bone marrow suppression Renal function (do not administer when CrCL <45 mL/min) Bullous and exfoliative skin toxicity Interstitial pneumonitis Radiation recall Fetal harm Most common adverse reactions (incidence ≥20%) with single agent use: fatigue, nausea, and anorexia

^a From U.S. Prescribing Information.

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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^b "+" indicates censored data or ongoing response.

The Applicant's Position:

The HER2-mutant NSCLC population is a molecularly defined population of patients whose survival outcome with therapies that are currently available appears to be numerically shorter than those of patients with other actionable driver mutations ([Mazieres et al. 2016](#); [Pillai et al. 2017](#); [Udagawa et al. 2019](#)). There is currently no approved targeted therapy for patients with metastatic NSCLC whose tumors contain HER2 mutations. Efficacy of currently approved treatment options for patients without actionable oncogenic driver mutations in the second-line setting is limited.

The limited efficacy of available therapies highlights the high unmet medical need for efficacious HER2-targeted therapy for patients with metastatic HER2-mutant NSCLC who have received at least 1 prior therapy, which might be addressed by new targeted agents.

The FDA's Assessment:

FDA agrees with the Applicant's description of the available therapies for patients with metastatic NSCLC with *HER2* (*ERBB2*) mutations who have received prior systemic therapy. Available second-line therapies include ramucurimab plus docetaxel, single agent chemotherapy, or anti-PD-(L)1 antibody therapy as a single agent for patients who are anti-PD-(L)1 naïve. No targeted agent has marketing authorization for the treatment of patients with NSCLC with *HER2* (*ERBB2*) mutations.

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3 REGULATORY BACKGROUND

3.1 U.S. REGULATORY ACTIONS AND MARKETING HISTORY

The Applicant's Position:

Enhertu® (fam-trastuzumab deruxtecan-nxki; T-DXd) was first approved by the Food and Drug Administration (FDA) on 20 Dec 2019 under accelerated approval for Biologics License Application (BLA) 761139 for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer (BC) who have received 2 or more prior anti-HER2-based regimens in the metastatic setting (5.4 mg/kg every 3 weeks [Q3W]). On 15 Jan 2021, ENHERTU was granted regular approval for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen (6.4 mg/kg Q3W). An efficacy supplement is currently under review for HER2-positive BC based on the results of DESTINY-Breast03.

The FDA's Assessment:

FDA agrees with the Applicant's position. On May 4, 2022, FDA granted traditional approval of T-DXd for 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 6 months of completing therapy based on the results of DESTINY-Breast03. This supplement satisfied Subpart H of 21CFR (Section 314.510) and served as the basis for verification of clinical benefit for the previously granted accelerated approval. An efficacy supplement is currently under review for HER2-low BC based on the results of DESTINY-Breast04.

3.2 SUMMARY OF PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY

The Applicant's Position:

A summary of key regulatory interactions related to T-DXd development in HER2-mutant NSCLC is provided in [Applicant - Table](#).

Applicant - Table 2: Key Regulatory Interactions Related to this sBLA

Date	Regulatory Interaction
22 Mar 2018	IND 137009 for NSCLC was opened with Study DS8201-A-U204 (Study U204, DESTINY-Lung01)
22 Jan 2020	Type C meeting to discuss the potential for data from Study U204 (DESTINY-Lung01) to support an sBLA under accelerated approval for T-DXd for the treatment of patients with HER2-mutant NSCLC

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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14 May 2020	Breakthrough Therapy Designation granted for the treatment of patients with metastatic NSCLC whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy.
07 Jul 2020	Type B, EOP2 meeting to discuss the study design of DS8201-A-U206 (Study U206, DESTINY-Lung02) (b) (4)
10 Sep 2021	Type B, pre-sBLA meeting to share and discuss the results from DS8201-A-U204 to support submission of an sBLA. Agreement reached on the structure, format, and content of the sBLA. Daiichi Sankyo committed to sharing plans for sBLA submission regarding dose selection.
14 Oct 2021	Agreement to submit sBLA with results from Study U204 (b) (4)

The FDA's Assessment:

FDA generally agrees with the Applicant's position. During the September 10, 2021, pre-sBLA meeting FDA indicated the Applicant had not adequately explored the proper dose of T-DXd for the treatment of patients with *HER2*-mutated NSCLC. While T-DXd appeared reasonably likely to provide clinical benefit and address significant unmet need for patients with *HER2*-mutated NSCLC, FDA expressed concern regarding the risk of ILD/pneumonitis with T-DXd in patients with refractory NSCLC who are particularly vulnerable to pulmonary toxicity. During an *ad hoc* meeting initiated by the FDA on October 14, 2021, FDA ultimately agreed the Applicant may submit an sBLA based on results (b) (4) from Study U204 but also strongly advised there should be ongoing, simultaneous enrollment to Study U206 to compare the 5.4 mg/kg and 6.4 mg/kg doses for dose optimization. During review of the sBLA, results from Study U206 became available, which demonstrated similar efficacy with reduced toxicity at the 5.4 mg/kg dose compared to the 6.4 mg/kg dose. Overall, results from Study U206 and Study U204 support approval of the 5.4 mg/kg dose.

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4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

No clinical sites were inspected for this supplemental application.

4.2 PRODUCT QUALITY

No new CMC information was provided in the supplemental application. Refer to CDER's Quality Review from the original BLA submission.

4.3 CLINICAL MICROBIOLOGY

No clinical microbiology data were submitted in the supplemental application.

4.4 DEVICES AND COMPANION DIAGNOSTIC ISSUES

Refer to the CDRH review by Drs. Deb Chatterjee, Kamesh Bikkavilli, Soma Ghosh, Francisca Reyes Turcu, and Wendy Rubinstein for full details.

The applicant partnered with Daiichi Sankyo to submit a PMA of the Oncomine™ Dx Target Test (P160045/S035) for the qualitative detection of *ERBB2* activating mutations (single nucleotide variants [SNVs] and exon 20 insertions) in formalin-fixed, paraffin-embedded (FFPE) tumor tissue from patients with NSCLC to identify patients who may benefit from treatment with ENHERTU® (fam-trastuzumab deruxtecan-nxki). There was another PMA (P200010/S008) for the Guardant360 CDx for the detection of *ERBB2* activating mutations in circulating cell-free DNA (cfDNA) in plasma to identify patients with NSCLC who may benefit from treatment with ENHERTU® (fam-trastuzumab deruxtecan-nxki). Patients with NSCLC whose FFPE tissue or plasma sample produce a positive test result for the presence of *ERBB2* activating mutations are eligible for treatment with the ENHERTU.

There were 91 patients enrolled in the DS8201-A-U204 (DESTINY-Lung01) clinical study based on detection of *ERBB2* activating mutations in tumor tissue by the clinical trial assay (CTA). The CTA was performed locally through testing of an archival or fresh tumor tissue sample analyzed by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent laboratory performing testing to Good Laboratory Practice (GLP) standard. The DS8201-A-U204 clinical study did not include patients negative for *ERBB2* mutations. A clinical bridging study was performed to demonstrate the concordance/agreement (PPA, Positive Percent Agreement and, NPA, Negative Percent Agreement) between the CTA vs the Oncomine™ Dx Target Test as

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well as to establish the clinical validity of the Oncomine™ Dx Target Test. Of the 91 patients with *ERBB2* mutations, 49 patients had valid Oncomine™ Dx Target Test results available (48 samples were CTA+, Oncomine™ Dx Target Test+ while one sample was CTA+, Oncomine™ Dx Target Test negative), and 42 patients had samples that were unevaluable. Thus, the analysis of clinical effectiveness was based on a bridging study using 49 patient samples that were evaluable by the Oncomine™ Dx Target Test companion diagnostic (CDx). The PPA of the Oncomine™ Dx Target Test to the CTA was calculated by assessing concordance by testing 49 CDx evaluable samples that were CTA+ in the clinical study, in addition to two CTA+ samples obtained from commercial sources; the PPA was found to be 98% (50/51). The NPA was estimated to be 100% (107/107), between the CTA and Oncomine™ Dx Target Test by testing negative samples that were commercially procured that yielded valid results. Clinical efficacy of ENHERTU® for the *ERBB2* activating mutation positive population identified by the Oncomine™ Dx Target Test (HR = 58.3% [n=28/48], 95% CI: 43.3% - 72.4%) was similar to the clinical efficacy in the DS8201-A-U204 cohort 2 (HR = 54.9% [n=50/91]; 95% CI: 44.2% - 65.4%).

A clinical bridging study was also performed to demonstrate the concordance between the CTA and the Guardant360 CDx as well as to establish the clinical validity of the Guardant360 CDx. The PPA of the Guardant360 CDx plasma test to CTA was assessed for the Guardant360 CDx evaluable samples (89 from the efficacy population in addition to one sample externally procured) and was 91% (82/90). The lower PPA may be in part attributed to variables such as low tumor shedding. The NPA between the Guardant360 CDx and the CTA obtained by testing commercially procured samples was found to be 100% (110/110). The observed ORR for the Guardant360 CDx positive samples was 58.0% (95% CI 46.5% - 68.9%) which is similar to that for the full primary population from the DS8201-A-U204 clinical study (54.9%, 95% CI: 44.2% - 65.4%).

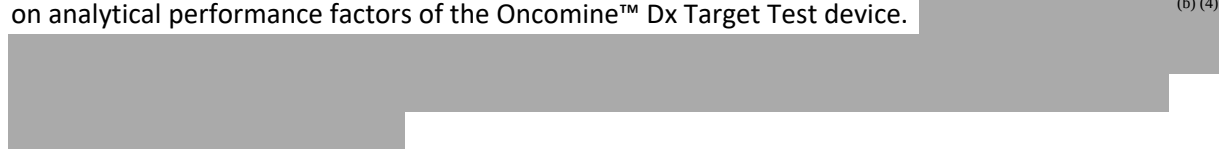
Since the PPA of the plasma test when compared to tissue results is 91%, a subset of patients that test negative by plasma may have a tissue positive result. For this reason, patients whose plasma sample produces a negative result using Guardant360 CDx test should be reflexed to testing for the presence of *ERBB2* activating mutations with FFPE tumor tissue.

Note: The efficacy of ENHERTU® was evaluated in the Daiichi Sankyo DS8201-A-U204 (n=91, and subject of these two PMAs) and DS8201-A-U206 (n=52) studies. ENHERTU® was evaluated at two dose levels (DS8201-A-U204 [6.4 mg/kg] and DS8201-A-U206 [5.4 mg/kg and 6.4 mg/kg]). The observed ORR for both Oncomine™ Dx Target Test positive samples (58.3%) and Guardant360 CDx positive samples (58.0%) are similar to the ORR for the DS8201-A-U206 study (57.7%, 95% CI: 43.2% - 71.3%). The duration of response (DOR) in patients that were ODxT Test+/CTA+ was 12 months, compared to 9.3 months for the CTA+, DS8201-A-U204 Cohort 2 population. The duration of response (DOR) for the Guardant360 CDx clinical efficacy population was 9.3 months (95% CI: 5.7, 18.2). The DOR for the DS8201-A-U204 study (DESTINY-Lung 01) was 9.3 months which is similar to the DOR for the DS8201-A-

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U206 study (DESTINY-Lung 02) of 8.7 months.

The data support the reasonable assurance of safety and effectiveness of the devices when used in accordance with the indications for use. The use of these devices to aid clinicians in identifying patients with NSCLC who may be eligible for treatment with ENHERTU® based on a *ERBB2* activating mutation detected result is expected to provide a benefit with ORR of about 58.3% for the Oncomine™ Dx Target Test and 58.0% for the Guardant360 CDx. There is some uncertainty to this assessment based primarily on analytical performance factors of the Oncomine™ Dx Target Test device. (b) (4)

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In summary, considering all factors including conditions of approval (post-market actions), the benefits of the use of Oncomine™ Dx Target Test and Guardant360 CDx in patients with NSCLC containing *ERBB2* activating mutations are judged to outweigh the risks.

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5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1 EXECUTIVE SUMMARY

Enhertu (DS-8201a; fam-trastuzumab deruxtecan-nxki) is a human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate. The antibody is a humanized anti-HER2 IgG1 (MAAL-9001) and is connected to the payload MAAA-118d (DXd), which is a topoisomerase I inhibitor, via a cleavable linker. The Applicant evaluated the effect of MAAA-1181d on various receptors, channels, transporters, and enzymes to determine off-target binding and activity of the payload. No significant response of MAAA-1181d at 10 µmol/L occurred based on criteria of significant level set as ≥50% inhibition on receptors, channels, transporters, and enzymes. In addition, the Applicant evaluated the in vivo antitumor activity of fam-trastuzumab deruxtecan-nxki against non-small lung cancer (NSCLC) tumors with *HER2* wild type (WT) or *HER2* mutations to support the proposed indication for this supplemental BLA. In general, a single administration of intravenous fam-trastuzumab deruxtecan-nxki to tumor bearing mice had antitumor activity against *HER2*- WT and mutated NSCLC tumors compared to vehicle control. The antitumor activity was greater in *HER2* mutant expressing tumors compared to *HER2* WT expressing tumors. Fam-trastuzumab deruxtecan-nxki is thought to exert its pharmacological activity through antibody binding to *HER2* resulting in internalization of the *HER2*/ADC complex and then lysosome trafficking of the complex and drug linker cleavage followed by payload release to tumor cells. To support this pharmacological activity in NSCLC, the Applicant showed that fam-trastuzumab deruxtecan-nxki had increased internalization in *HER2* mutant expressing cells compared to *HER2* wild type cells.

Primary pharmacology, pharmacokinetic, general toxicology studies of up to 3 months duration in rats and monkeys, and genetic toxicology studies with fam-trastuzumab deruxtecan-nxki, MAAA-1181a, and MAAL-9001 were previously reviewed in 2019 by the FDA with the original BLA submission for the *HER2*-positive breast cancer indication. Based on the data provided in the current supplement, no changes are warranted for the label for Enhertu. Overall, from the nonclinical perspective, the nonclinical data submitted to this supplement are adequate to support the approval of Enhertu for the proposed indication.

5.2 REFERENCED NDAs, BLAs, DMFs

The Applicant's Position:

Reference is made to the original BLA 761139 submitted on 29 Aug 2019 and approved on 20 Dec 2019. With this application, new pharmacology studies addressing *HER2*-mutant NSCLC to support the current application are provided.

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5.3 PHARMACOLOGY

Primary pharmacology

The FDA's Assessment

To support the supplemental BLA application for the treatment of patients with non-small cell lung cancer (NSCLC), the Applicant submitted studies evaluating the antitumor activity of fam-trastuzumab deruxtecan-nxki (DS-8201a) in xenograft models of NSCLC with *HER2* WT or *HER2* mutations. In Study p200604, a single intravenous dose of fam-trastuzumab deruxtecan-nxki to mice bearing subcutaneous NSCLC tumors expressing human WT *HER2* on Day 0 resulted in tumor growth inhibition (TGI) of 14, 34, and 79% for 1, 3, and 10 mg/kg fam-trastuzumab deruxtecan-nxki, respectively, compared to vehicle treated controls on Day 21. In mice bearing tumors with *HER2* mutations (S310F, V659E, G660D, R678Q, V697L, L755S, L755P, D769Y, A775_G776insYVMA, G776delinsVC, G776_V777insVGC, V777_G778insGSP, V777L, V842I, and T862A), fam-trastuzumab deruxtecan-nxki led to dose dependent TGI ranging from 19-98% compared to controls. Additionally, in a NSCLC cell line harboring the *HER2* G776delinsVC mutation, fam-trastuzumab deruxtecan-nxki led to TGI ranging from 96-99% compared to controls. In general, fam-trastuzumab deruxtecan-nxki had greater antitumor activity against *HER2* mutant-containing tumors than *HER2* WT tumors.

In Study cy20-h009-r01, investigators evaluated the internalization of fam-trastuzumab deruxtecan-nxki after binding to its target, *HER2*, in human NSCLC cell lines expressing WT or mutated *HER2*. Internalization activity was determined by evaluating levels of fam-trastuzumab deruxtecan-nxki on the cell surface by flow cytometry after incubation of cell lines with fam-trastuzumab deruxtecan-nxki and then a fluorescently conjugated secondary antibody. Results indicated that fam-trastuzumab deruxtecan-nxki internalization in cells expressing several *HER2* mutations was significantly higher than in NCI-H322 cells expressing *HER2* WT, potentially supporting the increased antitumor activity in *HER2* mutant tumor compared to those with *HER2* WT.

Secondary Pharmacology

The Applicant's Position:

In vitro pharmacological actions of DXd were evaluated on a total of 86 receptors, channels, transporters, and enzymes. DXd showed no significant response (within 50% inhibition of baseline) to any of the 86 targets at 10 µmol/L, indicating no relevant off-target activity.

The FDA's Assessment:

The FDA generally agrees; in Study TW04-0008917, no significant response of MAAA-1181d at 10 µmol/L

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occurred on receptors, channels, transporters, and enzymes that were evaluated based on criteria of significant level set as $\geq 50\%$ inhibition.

Safety Pharmacology

The Applicant's Position:

No new information is provided in the current application.

The FDA's Assessment:

The FDA agrees.

5.4 ADME/PK

The Applicant's Position:

No new information is provided in the current application.

The FDA's Assessment:

The FDA agrees.

5.5 TOXICOLOGY

The Applicant's Position:

No new information is provided in the current application.

The FDA's Assessment:

The FDA agrees.

X

X

Stephanie L. Aungst, PhD

Claudia P. Miller, PhD

Primary Reviewer

Supervisor

Enhertu® (fam-trastuzumab deruxtecan-nxki)

6 CLINICAL PHARMACOLOGY

6.1 EXECUTIVE SUMMARY

The FDA's Assessment:

Fam-trastuzumab deruxtecan (T-DXd) is an antibody drug conjugate (ADC) targeting HER2-positive expressing cells. The payload (MAAA-1181a or DXd) is a DNA topoisomerase inhibitor. The Applicant is seeking approval of T-DXd for the treatment of patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy. The recommended dosing regimen is 5.4 mg/kg as an IV infusion (90 min) once every 3 weeks (Q3W).

The clinical pharmacology review focused on evaluation of the recommended dosage 5.4 mg/kg Q3W. This dosing regimen is supported by the efficacy and safety results of a Phase 2 Study U206 with comparison of the recommended dosage 5.4 mg/kg Q3W versus a higher dosage 6.4 mg/kg Q3W, (b) (4) Together with population PK and exposure-response analyses, the safety and efficacy from Study 206 support a more favorable benefit:risk assessment profile for T-DXd in patients with HER2-mutant NSCLC at the 5.4 mg/kg Q3W dosage versus the 6.4 mg/kg Q3W dosage.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information submitted in BLA761139 (S-0021). This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in FDA - Table 3.

FDA - Table 3. Key Clinical Pharmacology Review Issues by FDA

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	- The primary evidence of effectiveness comes from Study DESTINY-Lung02 (U206), an ongoing global, multicenter, randomized Phase 2 dose optimization study comparing T-DXd 5.4 mg/kg Q3W (N=102) versus 6.4 mg/kg Q3W (N=50) in patients with metastatic HER2 mutant NSCLC after at least one regimen of prior anticancer therapy that must have contained platinum-based chemotherapy. - The supportive evidence of effectiveness comes from the following two studies, where T-DXd was administered at 6.4 mg/kg Q3W:

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	<u>Study DESTINY-Lung01 (U204) Cohort 2:</u> An ongoing international, open-label, multicenter, single-arm Phase 2 study. In Cohort 2d, 91 patients with previously treated metastatic HER2-mutant non-squamous NSCLC received T-DXd at 6.4 mg/kg Q3W. <u>Study DS8201-A-J101 (J101) Cohort 2d:</u> A first-in-human, multicenter, dose escalation and dose expansion clinical trial of T-DXd in patients with advanced solid tumors. In dose expansion Cohort 2d, 11 patients with HER2 mutant NSCLC were treated at T-DXd 6.4 mg/kg Q3W.
General Dosing instructions	The Applicant's proposed recommended dosage of T-DXd is 5.4 mg/kg as IV infusion once every 3 weeks (Q3W). This dosage is considered acceptable based on the following assessment: The efficacy results suggest a comparable profile to the higher dosage of 6.4 mg/kg Q3W in Study U206, where the ORR was 53.8% at 5.4 mg/kg Q3W and 42.9% at 6.4 mg/kg Q3W in a prespecified early analysis cohort. The safety results suggest an improved profile as compared to higher dosage of 6.4 mg/kg Q3W in U206. Particularly, the TEAEs leading to dose reduction was 11.8% at 5.4 mg/kg Q3W and 42.9% at 6.4 mg/kg Q3W in the prespecified early analysis cohort. Exposure-response analysis for efficacy suggests a lack of clinically significant relationships for ORR, based on data from Studies J101, U204, and U206 in the target patient population. Exposure-response analysis for safety suggests a positive relationship for Any Grade ILD, Grade 3+ TEAEs and serious TEAEs, based on data from 9 studies (J101, J102, A103, A104, U201, J202, U204, U205, U206) in all patients who received T-DXd. The linear pharmacokinetics (PK) of T-DXd cover the therapeutic dose range, and the generally comparable exposure at the same dose level for patients with NSCLC in the current submission and patients with breast cancer (approved at 5.4 mg/kg Q3W).
Immunogenicity	Overall, 2.1% (27/1311) of patients were identified with having treatment-emergent anti-drug antibodies (ADA), and 0.1% (1/1311) of patients were identified as having neutralizing antibodies against T-DXd.
Labeling	Overall, the proposed labeling recommendations are acceptable and contingent upon the Applicant's agreement with FDA's revisions to the

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	labeling. Clinical pharmacology labeling recommendations are detailed in Sections 6.2, 8.6, 8.7, and 12.3.
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6.2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Presentation of Data:

The clinical pharmacology profile of T-DXd was previously reported in the initial BLA in BC (initial BC application) based on Studies DS8201-A-J101 (J101), DS8201-A-J102 (J102), DS8201-A-A103 (A103), DS8201-A-A104 (A104), and DS8201-A-U201 (U201). Clinical pharmacology of T-DXd has been updated to include data from subjects with HER2-positive gastric cancer (GC) and HER2-overexpressing or HER2-mutant NSCLC from Studies DS8201-A-J202 (J202), DS8201-A-U205 (U205), and U204.

The population pharmacokinetics (PopPK) analysis was updated based on data pooled from the 8 studies mentioned above. The update to the established PopPK model for T-DXd and DXd was conducted to include data from Study U204, and assess the impact of potential intrinsic covariates on the pharmacokinetics (PK) of T-DXd and DXd, to estimate individual posthoc PK parameters for use in subsequent exposure-response (ER) analyses, and to compare exposures among subpopulations of interest.

ER analysis for efficacy was performed in NSCLC subjects (HER2-mutant and -overexpressing) as well as across cancer types from 5 studies (Study J101, U201, J202, U204, and U205) and were conducted using multiple endpoints, including ORR, best tumor response (BTR), and time course of sum of diameter (SoD). ER analysis for safety was conducted on the same integrated dataset that was used for PopPK analysis. The ER analysis for safety was conducted using the following safety endpoints: adverse events (AEs) associated with study drug discontinuation, AEs associated with dose reduction, AEs associated with study drug interruption, ≥Grade 3 AEs, serious adverse events (SAEs), any grade and ≥Grade 3 (lab-defined) anemia, neutrophil count decreased, platelet count decreased, any grade and Grade ≥3 drug-related interstitial lung disease (ILD) that was adjudicated by the independent ILD adjudication committee (AC), and ≥Grade 2 (lab-defined) left ventricular ejection fraction (LVEF) decreased. For immunogenicity analysis, the analysis set consisted of data used for PopPK analysis plus data from Study DS8201-A-U302 (Study U302). Refer to Section 6.3.1 for details.

The Applicant's Position:

The clinical pharmacology of T-DXd is well characterized. The PopPK analysis indicated that dose

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adjustments based on covariates or for special populations are not recommended. Based on PopPK analyses, T-DXd and DXd exposures were similar across HER2-mutant or HER2-overexpressing NSCLC and BC at the same dose. The ER analysis for efficacy predicted no clinically meaningful differences in ORR or BTR between the 5.4 mg/kg and 6.4 mg/kg Q3W regimens for HER2-mutant NSCLC subjects. ER analysis for safety predicted a numeric improvement in safety profile with the T-DXd 5.4 mg/kg Q3W dose relative to the T-DXd 6.4 mg/kg Q3W dose. The prevalence of immunogenicity was low.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

In addition to the 8 studies mentioned above, Study U206 (cut off date March 24, 2022) was also included in the Applicant's updated population PK model and exposure-response analysis report, submitted during the review of the current supplement BLA. The Applicant's updated population PK model together with E-R analysis support the use of T-DXd at 5.4 mg/kg Q3W in patients with HER2-mutant NSCLC. See Section 6.2.2 the section *General Dosing and Therapeutic Individualization* below for details.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant's Presentation of Data:

The recommended dosing regimen for T-DXd in subjects with unresectable or metastatic HER2-mutant NSCLC who have received a prior systemic therapy is (b) (4) Q3W. This dose recommendation was based on the totality of the observed efficacy and safety data from the first-in-human Phase 1 study (J101) and Phase 2 study (U204), PopPK and ER safety analyses from 8 studies (J101, J102, A103, A104, U201, J202, U204, and U205), and ER efficacy analyses including NSCLC data from Studies J101 and U204.

Based on PopPK analyses, exposure to T-DXd and DXd was similar across HER2-mutant or HER2-overexpressing NSCLC and BC subjects at the same dose.

Based on pooled data for subjects with HER2-mutant NSCLC (N = 102), ORR based on independent central review (ICR) was 56.9% (95% confidence interval [CI]: 46.7, 66.6), median DoR was 9.7 months

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(95% CI: 6.9, 14.1), median PFS was 8.3 months (95% CI: 6.9, 11.9), and median OS was 17.8 months (95% CI: 14.0, 22.1). The ER analyses for efficacy also predicted clinically meaningful efficacy (ORR or BTR) for 6.4 mg/kg and 5.4 mg/kg doses in HER2-mutant NSCLC. A small numeric reduction (~1%) in ORR or BTR was predicted for the 5.4 mg/kg dose compared to the 6.4 mg/kg dose in HER2-mutant or HER2-overexpressing NSCLC. ER modeling of time course of SoD also predicted small differences in BTR (~5% to 8.6%) between 5.4 mg/kg and 6.4 mg/kg regimens (assuming either no dose reductions or dose reductions following the pattern in the observed data) for both the HER2-mutant and HER2-overexpressing NSCLC. It is noteworthy that these simulations for SoD time course do not take into account treatment discontinuations and dropouts for these dose levels.

ER analysis for safety indicated an exposure-related increase in rate of events and a similar rate of events in HER2-mutant and HER2-overexpressing NSCLC, except for 12% more SAEs in HER2-overexpressing NSCLC than HER2-mutant NSCLC at T-DXd 6.4 mg/kg. Key safety parameters trended towards lower AE incidence (up to 8% lower predicted incidence) at 5.4 mg/kg compared with 6.4 mg/kg in NSCLC. Modeled rates of hematological AEs were lower (1% to 17%) and ≥Grade 3 AEs, SAEs, and discontinuations associated with AEs were slightly higher (6% to 11%) following T-DXd 6.4 mg/kg Q3W in NSCLC relative to T-DXd 5.4 mg/kg Q3W in BC. Modeled rates of ILD at 180 days were higher (~2.5% to 5%) following the 6.4 mg/kg T-DXd Q3W regimen in NSCLC subjects compared with 5.4 mg/kg T-DXd Q3W in BC or NSCLC subjects. Overall, the safety ER analyses predicted a small improvement in the incidence of key safety parameters at 5.4 mg/kg than 6.4 mg/kg in NSCLC.

The Applicant's Position:

Clinically meaningful efficacy (ORR, DoR, PFS) was observed in subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Studies J101 and U204. Observed safety data in subjects with HER2-mutant and HER2 overexpressing NSCLC in Studies U204 and J101 support a generally acceptable safety profile at the (b) (4) dose. The totality of observed safety and efficacy data and the ER analyses for safety and efficacy support that T-DXd (b) (4) dose has a positive benefit-risk profile in subjects with unresectable or metastatic HER2-mutant NSCLC who have received a prior systemic therapy, which is a patient population with a high unmet medical need.

The FDA's Assessment:

FDA disagrees with the Applicant's original position that (b) (4) Q3W is the optimized dosage in patients with HER2-mutant NSCLC. With the updated clinical data from Study U206, as well as updated population PK and exposure-response analysis, FDA recommends approval of T-DXd at 5.4 mg/kg Q3W in the target patient population, based on the following:

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Efficacy:

In Study 206, in a Prespecified Early Cohort, the results suggest a favorable efficacy profile at 5.4 mg/kg Q3W. With regard to ORR by blinded independent review committee (BIRC), the results were 53.8% (95% CI: 39.5, 67.8) for the T-DXd 5.4 mg/kg Q3W dosage in 52 patients and 42.9% (95% CI: 24.5, 62.8) for the T-DXd 6.4 mg/kg Q3W dosage in 28 patients. These efficacy results for the 5.4 mg/kg dose level were comparable to that based on a pooled data analysis of Studies J101 and U204 (ORR: 56.9%) for the 6.4 mg/kg dose level.

Safety:

In Study 206, in both the Safety Analysis dataset and the Prespecified Early Cohort, the results suggest an improved safety profile at 5.4 mg/kg Q3W as compared to that at 6.4 mg/kg Q3W. The safety results suggest an improved profile as compared to the higher dosage 6.4 mg/kg Q3W in study U206. Comparing the T-DXd 5.4 mg/kg group to the 6.4 mg/kg dose group, with regard to TEAEs leading to dose reduction, the rate was 12.9% (13/101) (5.4 mg/kg Q3W) versus 30.0% (15/50) (6.4 mg/kg Q3W) in the Safety Analysis dataset, and 15.7% (8/51) (5.4 mg/kg Q3W) versus 46.4% (13/28) (6.4 mg/kg Q3W) in the Prespecified Early Cohort, respectively. With regard to the incidence of ILD, the rate was 5.0% (5/101) (5.4 mg/kg Q3W) versus 14.0% (7/50) (6.4 mg/kg Q3W) in Safety Analysis Set, and 5.9% (3/51) (5.4 mg/kg Q3W) versus 17.9% (5/28) (6.4 mg/kg Q3W) in the Prespecified Early Cohort, respectively.

Exposure-response analysis for efficacy:

In the Applicant's updated E-R analysis for efficacy, data in patients with HER2-mutant NSCLC were included from Studies J101, U204 (updated data), and U206 (new data) to evaluate the correlation of ORR versus C_{avg} at Cycle 2. Based on the analysis, overall results exhibited no significant E-R relationship for ORR vs. C_{avg} of T-DXd. The flat E-R relationship for efficacy endpoints may imply that the effectiveness of T-DXd reached a plateau, supporting the appropriateness of the lower dosage at 5.4 mg/kg Q3W. (FDA - Figure 1)

Exposure-response analysis for safety:

In the Applicant's updated E-R analysis for safety, data in patients with HER2-mutant NSCLC were included from 9 studies (J101, J102, A103, A104, U201, J202, U204 – updated data, U205, and U206 – new data, U302, U303) to characterize E-R for safety relationships for the following AE endpoints: occurrence of any AE, Grade ≥ 3 , occurrence of any serious AE, time to first occurrence of drug-related adjudicated interstitial lung disease (ILD) AE, any grade.

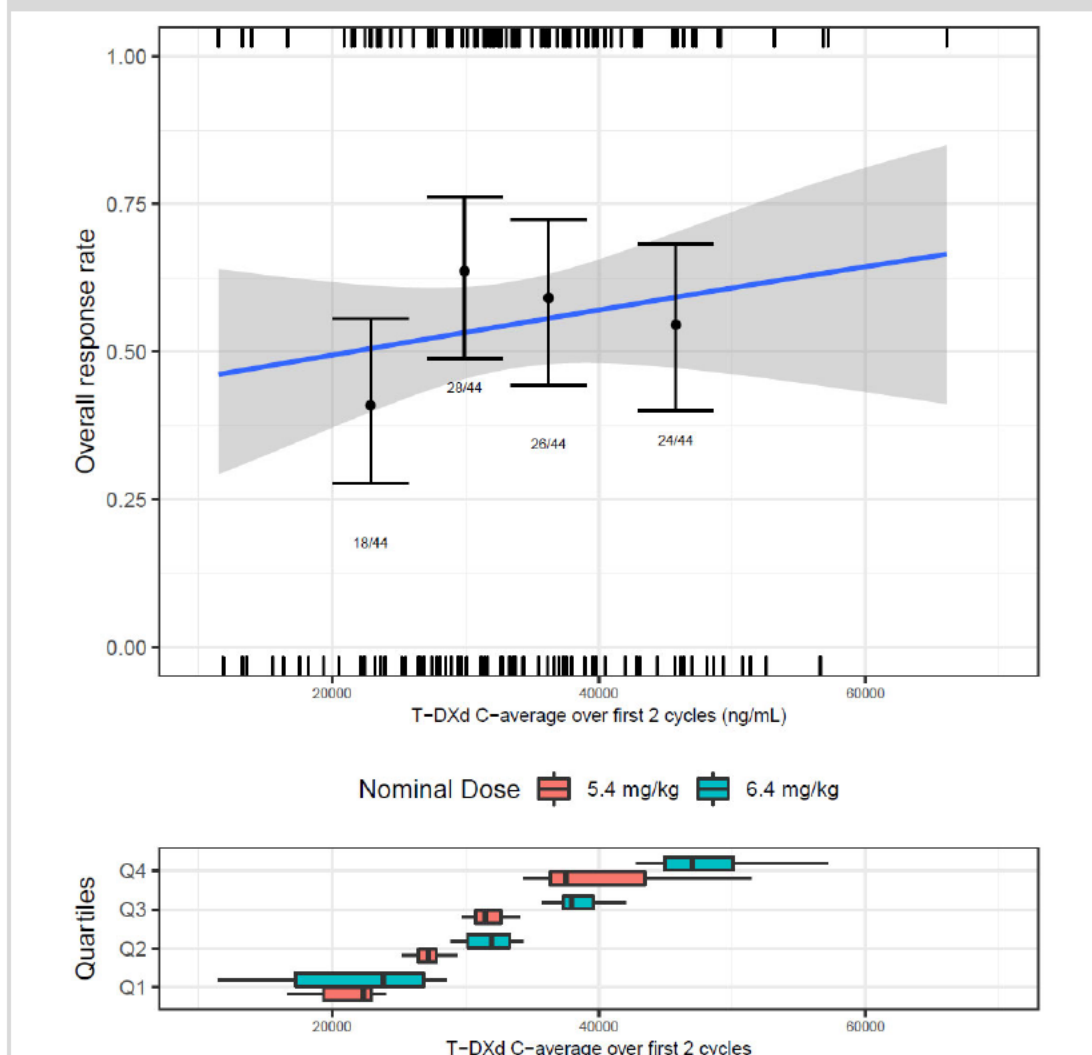
The E-R for safety results indicated a positive E-R relationship for any AEs grade ≥ 3 and any serious AE versus DXd C_{avg} to the time of event in the pooled population across all evaluated dosages (FDA - Figure 2, FDA - Figure 3). The E-R between

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AUC_{ss} and ILD any grade incidence also showed a positive relationship, and the survival analysis showed that shorter ILD any grade event-free survival was associated with higher AUC_{ss} (FDA - Figure 4

FDA - Figure 4). These findings further support the appropriateness of lower dosage of 5.4 mg/kg Q3W.

FDA - Figure 1. Applicant's update E-R Analysis for ORR vs PK Exposure $C_{avg, cycle 2}$



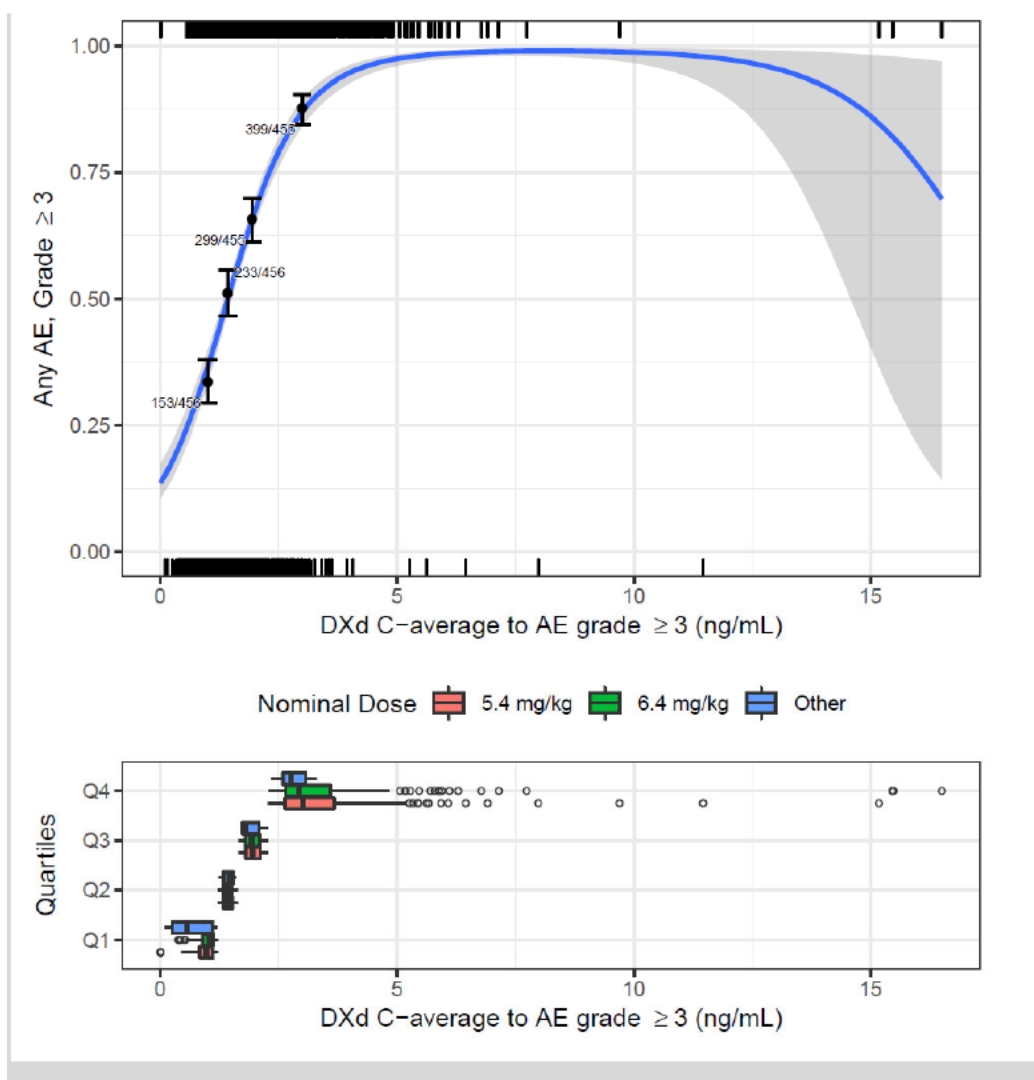
Dashed line along the x-axis indicates responder (one) and non-responder (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that are responders within each

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quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion. Numbers represent responders and total subjects within each quartile. Plot excluded one subject with exposure value greater than 100,000 ng/mL. Bottom panel shows distribution of exposure by quartile within each nominal dose of HER2-mutant NSCLC population.

Source: Applicant's ER Topline Efficacy Report titled Update of Exposure-Response Analysis of Efficacy of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer, Report Number: DSI1501F-EE-BriefComm-v1.0-Final, Figure 3.

FDA - Figure 2. ES analysis of any AE, Grade ≥ 3 : observed and model-fitted rate of AE associated with DXd Cavg through the time of first event



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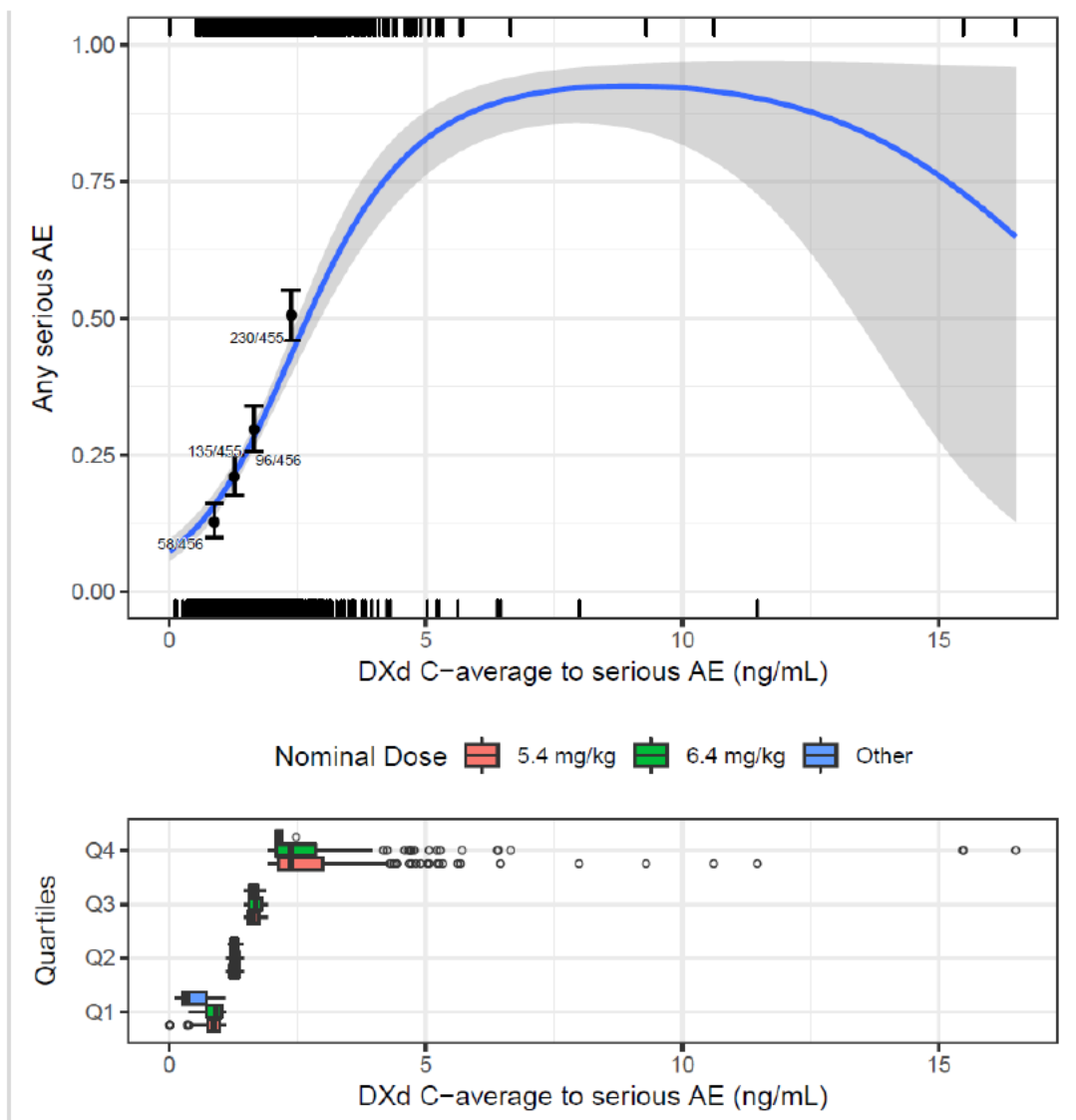
Dashed line along the x-axis indicates ILD any grade event (one) and no event (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that have event within each quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion. Numbers represent responders and total subjects within each quartile.

Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors, Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 2.

FDA - Figure 3. ES analysis of serious AE: observed and model-fitted rate of AE associated with Dxd Cavg through the time of first event.

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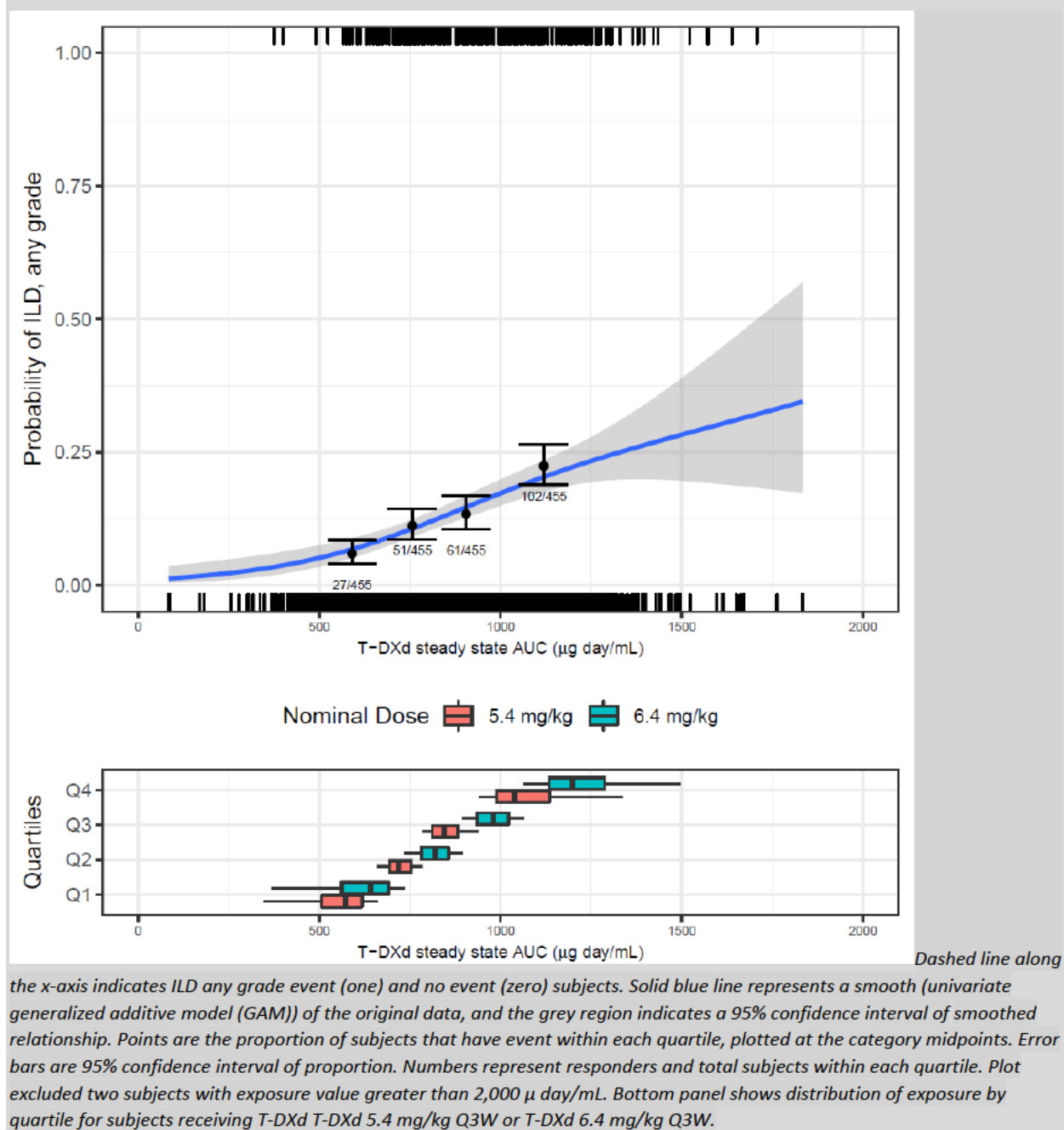
Dashed line along the x-axis indicates ILD any grade event (one) and no event (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that have event within each quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion. Numbers represent responders and total subjects within each quartile.

Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 11.

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FDA - Figure 4. Safety Endpoint - ILD Any Grade Incidence versus PK Exposure - AUCss.



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Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors, Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 2.

Based on the above, the totality of observed safety and efficacy data and the ER analyses for safety and efficacy support that the T-DXd dosage of 5.4 mg/kg Q3W has a more favorable benefit-risk profile versus the 6.4 mg/kg Q3W dosage in patients with unresectable or metastatic HER2-mutant NSCLC who have received a prior systemic therapy.

Therapeutic Individualization

Data:

The effect of each intrinsic factor was evaluated using PopPK analysis, which showed that for T-DXd, body weight, baseline albumin, baseline tumor size, race-country, cancer type, and sex were statistically significant covariates affecting the clearance of T-DXd or the volume of distribution in the central compartment of T-DXd. For DXd, race-country, cancer type, formulation, age, baseline aspartate aminotransferase, baseline total bilirubin, coadministration of ritonavir and itraconazole, and body weight were statistically significant covariates affecting the clearance or the volume of distribution of DXd, consistent with prior PopPK analyses. NSCLC cancer type (BC, GC, and NSCLC were assessed in the analysis) was the only intrinsic factor that was additionally identified as a factor affecting the PK of T-DXd and DXd compared to previous PopPK analyses.

The Applicant's Position:

No therapeutic individualization for intrinsic or extrinsic factors is recommended. Results of the PopPK analysis indicate no clinically meaningful effects of any intrinsic factors on the exposures of T-DXd or DXd. No dose adjustments are required.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustments are recommended. Findings from the updated PopPK analysis showed that dose adjustments based on covariates for special populations are not recommended.

Outstanding Issues

Data:

No new information is provided in the current application.

The Applicant's Position:

None.

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The FDA's Assessment:

None.

6.3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Drug Product and General ADME Characteristics

The ADME characteristics of T-DXd are well characterized based on a series of nonclinical studies using human biomaterials and based on data from clinical Studies J101, J102, A103, A104, and U201 as described in the initial BLA in BC. One additional nonclinical study (Study TCRM-DMPK-2020-19) conducted after the initial BLA used cryopreserved hepatocytes and supported that DXd, at concentrations up to 30 nmol/L, did not show any induction potential or effect on metabolic activity of cytochrome P450 (CYP) 3A4, CYP1A2, or CYP2B6.

Population-pharmacokinetics analysis

In the final model for T-DXd:

Consistent with the previous PopPK analysis, the PK of T-DXd was adequately described by a 2-compartment model with linear elimination. The final model suggests that elimination clearance of T-DXd increases with higher body weight, baseline tumor size, and having GC or NSCLC or other cancers. Elimination clearance of T-DXd decreases with increasing albumin and in subjects in Japan. T-DXd central volume of distribution increases with higher body weight and having GC or being male, while T-DXd peripheral volume of distribution decreases in subjects from Japan.

In the final model for DXd:

Consistent with previous PopPK analyses of DXd, the PK of DXd was adequately described by a 1-compartment model with a 2-component, time-varying release rate from T-DXd. In the final model for DXd, elimination clearance of DXd increases with higher body weight and decreases with increasing baseline total bilirubin and aspartate aminotransferase, coadministration of itraconazole or ritonavir, and having GC or NSCLC or other cancers. DXd volume of distribution increases with higher body surface area, age, frozen liquid drug product 2 formulation. DXd volume of distribution decreases with the frozen liquid drug product 1 formulation, having NSCLC or other cancers, and for non-Asians.

For both T-DXd and DXd, the majority of covariates had effects contained within or marginally outside the 0.8 to 1.25 exposure ratio.

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Exposure-Response for Efficacy

In the ER analyses for efficacy, the relationship between the serum exposure of T-DXd and key efficacy endpoints were analyzed using model-based approaches. The analyses for ORR and BTR included data across cancer types (HER2-mutant NSCLC, HER2-overexpressing NSCLC, HER2-positive BC, and HER2-positive GC) as well as sensitivity analyses including NSCLC data (HER2-mutant or HER2-overexpressing) or only HER2-mutant NSCLC. The analyses of time course of SoD included data from HER2-mutant and HER2-overexpressing NSCLC subjects.

ER relationships for all endpoints from all modeling approaches were shallow. For ORR and BTR endpoints, the shallow relationship was robust to sensitivity analyses with different populations.

The predicted response rate in the HER2-mutant NSCLC population was 57.6% (90% credible interval: 49.2, 65.8) at the 6.4 mg/kg dose, compared to 56.4% (90% credible interval: 47.6, 64.8) at the 5.4 mg/kg dose with no clinically meaningful differences between the doses. Sensitivity analyses using only HER2-mutant NSCLC population or all NSCLC population (HER2-mutant or HER2-overexpressing) showed differences of -2.03% and -1.56% between the 6.4 mg/kg and 5.4 mg/kg dose levels, respectively.

The predicted BTR in the HER2-mutant NSCLC population was -45.5% (90% credible interval: -51.9, -38.6) at the 6.4 mg/kg dose compared to -44.4% (90% credible interval: -51.1, -37.5) at the 5.4 mg/kg dose, with a difference of 1.06% (90% credible interval: -3.45, 5.86) between the doses. Sensitivity analyses using only HER2-mutant NSCLC population or all NSCLC population (HER2-mutant or HER2-overexpressing) had differences in BTR of 3.41% and 2.00%, respectively. Consistent with HER2-mutant NSCLC, small differences in ORR and BTR were predicted for HER2-overexpressing NSCLC subjects between the 6.4 mg/kg and 5.4 mg/kg dosing regimens.

ER modeling of time course of SoD predicted small differences in BTR (approximately 5% to 8.5%) between 6.4 mg/kg and 5.4 mg/kg regimens (assuming either no dose reductions or dose reductions following the pattern in the observed data) for both the HER2-mutant and HER2-overexpressing populations. It is noteworthy that these simulations for time course of SoD do not take into account treatment discontinuations and dropouts for these dose levels.

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Exposure-Response for Safety

The ER analysis for safety was conducted using the safety endpoints as described in Section 6.1. ER safety relationships were generally consistent with previous ER analyses conducted to support approval of BC and GC indications.

- T-DXd steady state area under the concentration-time curve was correlated with treatment-emergent adverse events (TEAEs) associated with study drug discontinuation and any grade ILD, T-DXd steady state maximum serum concentration was correlated with $\geq$ Grade 2 LVEF decrease and $\geq$ Grade 3 ILD, and DXd average plasma concentration to the event time was correlated with the other TEAEs.
- Model-predicted AE rates were generally comparable between HER2-mutant and HER2-overexpressing NSCLC subjects at the same dose. Modeled HER2-overexpressing subjects had 12% more SAEs than HER2-mutant subjects at T-DXd 6.4 mg/kg Q3W.
- Model-predicted AE rates were lower (up to 8%) following the 5.4 mg/kg T-DXd Q3W regimen compared with 6.4 mg/kg T-DXd Q3W in HER2-mutant and HER2-overexpressing NSCLC subjects.
- Modeled rates of hematological AEs were lower (15% to 20% for any grade), and SAEs, $\geq$ Grade 3 AEs, and drug discontinuations associated with AEs were slightly higher (5% to 11% increase) following the 5.4 mg/kg T-DXd Q3W regimen in NSCLC subjects relative to 5.4 mg/kg T-DXd Q3W in BC subjects.
- Modeled rates of hematological AEs were lower (1% to 17%) and $\geq$ Grade 3 AEs, SAEs, and discontinuations associated with AEs were slightly higher (6% to 11%) following T-DXd 6.4 mg/kg Q3W in NSCLC subjects relative to T-DXd 5.4 mg/kg Q3W in BC subjects.
- Low oxygen saturation was identified as a potential covariate of increased Grade $\geq$ 3 ILD risk.
- Model-predicted rates of ILD at 180 days were higher (~2.5% to 5%) following the 6.4 mg/kg T-DXd Q3W regimen in NSCLC subjects compared with 5.4 mg/kg T-DXd Q3W in BC or NSCLC subjects.

Immunogenicity

Across the 9 clinical studies, the incidence of immunogenicity was low. Across all evaluated doses and tumor types, the incidence of treatment-emergent anti-drug antibody following treatment with T-DXd was 2.1% (27 of 1311 subjects). The incidence of neutralizing antibody against T-DXd was low (0.1% [1/1311]).

The Applicant's Position:

Findings from the PopPK analysis showed that dose adjustments based on covariates or for special populations are not recommended. Findings from the ER efficacy analysis support clinically meaningful efficacy of T-DXd at both 6.4 and 5.4 mg/kg doses in HER2-mutant NSCLC population and the difference in efficacy endpoints between 6.4 mg/kg and 5.4 mg/kg doses is

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not predicted to be clinically meaningful among subjects with HER2-mutant NSCLC. Findings from the ER safety analysis support that both T-DXd 5.4 mg/kg and T-DXd 6.4 mg/kg doses in subjects with NSCLC have a generally acceptable safety profile and a numeric improvement in safety profile was noted among subjects with NSCLC following treatment with the T-DXd 5.4 mg/kg Q3W dose compared to the T-DXd 6.4 mg/kg Q3W dose. Across all evaluated doses and tumor types, the incidence of treatment-emergent anti-drug antibody (2.1%; 27/1311 subjects) and neutralizing antibody (0.1%; 1/1311 subjects) following treatment with T-DXd was low. No relationship was identified between PK, efficacy, or infusion related reactions (as a measure of safety) and immunogenicity of T-DXd.

The FDA's Assessment:

FDA recommends the use of T-DXd at 5.4 mg/kg Q3W in patients with HER2-mutant NSCLC, based on efficacy, safety, population PK, and E-R analysis. See Section 6.2.2.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Refer to Sections 6.2.1 and 6.3.1.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness. The ER relationship for efficacy endpoints (ORR or BTR) for NSCLC patients was similar to other tumor types, such as BC or GC. The ER relationship for efficacy endpoints showed that T-DXd systemic exposures correlated with ORR, BTR as well as time course of SoD. These analyses predicted clinically meaningful efficacy at the 6.4 and 5.4 mg/kg doses in HER2-mutant NSCLC population and the difference in efficacy endpoints between 6.4 mg/kg and 5.4 mg/kg doses was not predicted to be clinically meaningful among subjects with HER2-mutant NSCLC. Results from the ER analysis for safety were generally consistent with the observed safety profile and indicated there was a correlation between T-DXd and DXd exposures and safety endpoints. Overall, these analyses support that T-DXd has a positive benefit-risk ratio at a 6.4 mg/kg dose Q3W in patients with unresectable or metastatic NSCLC who have a HER2 mutation and have received a prior systemic therapy.

The FDA's Assessment:

FDA recommends the use of T-DXd at 5.4 mg/kg Q3W in patients with HER2-mutant NSCLC, based on efficacy, safety, population PK, and E-R analysis. See Section 6.2.2.

Response in ERBB2 (HER2) Mutation Subgroups

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The presence of an ERBB2 (HER2) activating mutation in archival and/or freshly collected tumor tissue samples as determined by local testing was used for enrollment in Studies U206 (N=52), U204 Cohort 2 (N=91), and J101 Part 2d (N=11). Retrospective central testing results using the Oncomine Dx Target (ODxT) Test were available for 48 (53%) patients in Study U204. According to the Applicant, ERBB2 mutations were predicted to be activating (oncogenic or likely oncogenic) based on review of literature or public knowledge databases, such as PubMed, CKB, OncoKB, ClinVar, DoCM, and CIViC. The list of eligible mutations for inclusion in Studies U206 and U204 can be found in FDA - Table 4.

FDA - Table 4. Eligible ERBB2 (HER2) mutations in (A) Study U206 and (B) Study U204.

HER2 mutations	HER2 mutations
Exon 20 insertion (any) Tyr772_Ala775dup (Ala771_Tyr772insTyrValMetAla, Glu770_Ala771insAlaTyrValMetAla775_Gly776insTyrValMetAla) Ala775_Gly776insVal Ala775_Gly776insThrValMetAla (Tyr772_Val773insValMetAlaThr) Gly776delinsLeuCys Gly776delinsValCys Gly776_Val777insLeu Gly778_Ser779insCysValGly (Gly776_Val777insValGlyCys) Val777_Gly778insCysGly (Gly776_Val777delinsCysValCysGly), Val777_Ser779dup (Gly776_Val777insValGlySer, Ser779_Pro780insValGlySer) Gly778_Ser779insLeuProSer Gly778dup (Val777_Gly778insGly) Gly778_Pro780dup (Val777_Gly778insGlySerPro, Pro780_Tyr781insGlySerPro) Ser310Phe Ser310Tyr Arg678Gln Thr733Ile Leu755Ala Leu755Met Leu755Pro Leu755Ser Leu755Trp Ile767Met Asp769Asn Asp769His Asp769Tyr Gly776Cys Gly776Ser Gly776Val Val777Leu Val777Met Val777_Tyr778insCysGly Gly778_Ser779insLeuProSer Val777_Gly778insGly Gly776_Val777insValGlySer Val777_Gly778insGlySerPro Ser310Pro Ser310Tyr Ser310Phe Arg678Gln Thr733Ile Leu755Met Leu755Pro Leu755Ser Leu755Trp Asp769Asn Asp769His Asp769Tyr Gly778_Ser779insCysProGly (Val777_Gly778insGlyCysPro) Leu755_Glu757delinsSer Leu755_Thr759del Val777_Gly778insCysVal Ile767Phe Thr798Ile	Glu770_Ala771insAlaTyrValMet Ala771_Tyr772insTyrValMetAla Gly776delinsLeuCys Gly776Ser Gly776Cys Gly776delinsValCys Gly776Val Gly776Val777insLeu Val777Leu Val777Met Val777_Gly778insCysGly Gly778_Ser779insLeuProSer Val777_Gly778insGly Gly776_Val777insValGlySer Val777_Gly778insGlySerPro Ser310Pro Ser310Tyr Ser310Phe Arg678Gln Thr733Ile Leu755Met Leu755Pro Leu755Ser Leu755Trp Asp769Asn Asp769His Asp769Tyr

Sources: Study U206 and U204 protocols.

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The eligible ERBB2 mutation types included insertion/deletions (in/del) as well as single nucleotide variants (SNV) in exons 8, 19, and 20. In U206, the ERBB2 mutations were found in the extracellular domain (exon 8, N=3) and the kinase domain (exon 19, N=2; exon 20, N=47). In U204 Cohort 2, the ERBB2 mutations were found in the extracellular domain (exon 8, N=6) and the kinase domain (exon 19, N=4; exon 20, N=81). In J101 Part 2d, the ERBB2 mutations were found in the extracellular domain (exon 8, N=1), the transmembrane domain (exon 17, N=2), and the kinase domain (exon 20, N=8).

Patients with ERBB2 kinase domain mutations had ORRs of 53-58% in studies U206 and U204 and an ORR of 75% in the smaller supportive study J101 (Applicant - Figure 7, FDA - Table 5). An exploratory analysis by the reviewer to assess response by mutations in other ERBB2 domains found an ORR of 17-67% in patients with ERBB2 extracellular domain mutations. Two patients in study J101 had ERBB2 transmembrane domain mutations with an ORR of 50%. Analysis of response by mutation type showed an ORR of 51-58% (87.5% in J101) in patients with indels and 31-80% in patients with SNVs. Additionally, co-occurring mutations were observed in 3 patients: 1 patient with an ALK mutation in study J101 had a best response of PR; 1 patient in J101 with a BRAF mutation had a best response of PR; and 1 patient in U204 with an EGFR mutation had a best response of SD. Given that ENHERTU is an HER2-directed antibody-drug conjugate, an analysis of response by HER2 expression may have been informative. However, the limited data on HER2 expression in the ERBB2 mutant population of study U204 precluded such an analysis. As responses were observed across most ERBB2 activating mutation domains and types, further selection based on ERBB2 mutation subgroups is not warranted based on the available data.

FDA - Table 5. Response by ERBB2 (HER2) Activating Mutations and Domains

Study	ERBB2 (HER2) Mutation	N (%)	ORR
U206	Kinase Domain	49 (94)	53%
	Leu755Met	1	100%
	Leu755Ala	1	100%
	Glu770_Ala771insAlaTyrValMet	1	100%
	Tyr772_Ala775DUP (Ala771_Tyr772insTyrValMetAla, Glu770_Ala771insAlaTyrValMet)	27	41%
	Ala775_Gly776insVal	1	100%
	Ala775_Gly776insThrValMetAla	6	50%
	Gly776delinsValCys	8	63%
	Gly776Cys, Val777dup	1	100%
	Gly776_Val777delinsValCysAsp,	1	100%

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	c.2327_2331delinsTGTGTGAC		
	Val777_Gly778insCysGly	1	0%
	Gly778_Pro780dup (Val777_Gly778insGlySerPro)	1	100%
	Extracellular Domain Ser310Phe	3 (6)	67%
	Total	52	54%
U204 Cohort 2	Kinase Domain	85 (93)	58%
	Leu755Pro	2	50%
	Leu755Ser	1	100%
	Asp769His	1	0%
	Tyr772_Ala775dup	57	61%
	Ala775_Gly776insThrValMetAla	1	100%
	Gly776delinsValCys	9	44%
	Gly776Ser	1	0%
	Val777Leu	2	50%
	Gly778_Pro780dup	10	60%
	Gly778_Ser779insLeuProSer	1	0%
	Extracellular Domain	6 (7)	17%
	Ser310Phe	4	25%
	Ser310Tyr	2	0%
	Total	91	55%
J101 Part 2d	Kinase Domain	8 (73)	75%
	Tyr772_Ala775dup	6	83%
	Ala775_Gly776insVal	1	100%
	Gly778_Pro780dup	1	0%
	Transmembrane Domain Gly660Asp	2 (18)	50%
	Extracellular Domain Ser310Phe, Asp277Tyr	1 (9)	100%
	Total	11	73%

Source: Review analysis.

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6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Refer to Section 6.2.2.

The Applicant's Position:

The proposed dosing regimen for T-DXd, (b) (4) Q3W, is appropriate for subjects with unresectable or metastatic HER2-mutant NSCLC who have received at least 1 prior systemic therapy. The observed efficacy and safety data in subjects with HER2-mutant NSCLC and the ER analyses for efficacy and safety support that T-DXd (b) (4) dose in subjects with HER2-mutant NSCLC has a positive benefit-risk profile. The PopPK analysis support that none of the intrinsic factors evaluated had any clinically meaningful impact on T-DXd or DXd exposure and hence, no dose adjustments are needed based on intrinsic factors or for special populations.

The FDA's Assessment:

FDA recommends the use of T-DXd at 5.4 mg/kg Q3W in patients with HER2-mutant NSCLC, based on efficacy, safety, population PK, and E-R analysis. See Section 6.2.2.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Refer to Section 0.

The Applicant's Position:

Based on the PopPK analysis, none of the intrinsic factors evaluated had any clinically meaningful impact on T-DXd or DXd exposure and hence, no dose adjustments are needed.

The FDA's Assessment:

FDA agrees that no dose adjustment is recommended based on intrinsic factors or for special populations.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

No new information is provided in the current application.

The Applicant's Position:

No dose adjustment is needed for food-drug or drug-drug interactions.

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The FDA's Assessment:

None.

X

X

Primary Reviewer

Team Leader

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-021)

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7 SOURCES OF CLINICAL DATA

7.1 TABLE OF CLINICAL STUDIES

The Applicant's Presentation of Data:

An overview of the clinical studies supporting the efficacy and safety of T-DXd in HER2-mutant NSCLC is presented in Applicant - Table 6.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-021)

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Applicant - Table 6: Listing of Relevant Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety								
DS8201-A-U204 (Study U204, DESTINY-Lung01)	03505710	Phase 2, multicenter, non-randomized, open-label, 2-cohort	T-DXd IV infusion Q3W C1: 6.4 mg/kg C1a: 5.4 mg/kg C2: 6.4 mg/kg	<u>Primary:</u> ORR by ICR <u>Secondary:</u> DoR (by ICR and investigator), DCR (by ICR and investigator), PFS (by ICR and investigator), OS, ORR by investigator <u>Other:</u> PK, safety, immunogenicity, time to response, best percent change in the SoD for all target lesions per RECIST v1.1 (by ICR and investigator)	<u>DCO:</u> 03 May 2021 <u>Median treatment duration:</u> C1: 4.1 months (0.7-20.7) C1a: 4.8 months (0.7-9.6) C2: 6.9 months (0.7-26.4) <u>Median duration of study follow-up:</u> C1: 12.0 months (0.4-29.9) C1a: 6.3 months (0.6-10.0) C2: 13.1 months (0.7-29.1)	C1: 49 C1a: 41 C2: 91	Unresectable and/or metastatic HER2-overexpressing (IHC 3+ or IHC 2+) NSCLC or HER2-mutant NSCLC	20 centers 5 countries

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
DS8201-A-J101 (Study J101)	02564900	Phase 1, multicenter, non-randomized, open-label, multiple-dose, first-in-human in 2 parts: Dose Escalation (Part 1) and Dose Expansion (Part 2)	T-DXd IV infusion Q3W <u>Part 1:</u> ^a 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg <u>Part 2:</u> Parts 2a, 2b, and 2c: 5.4 or 6.4 mg/kg Parts 2d and 2e: 6.4 mg/kg	<u>Part 1:</u> <u>Primary:</u> Safety, tolerability, MTD/ recommended Phase 2 dose <u>Secondary:</u> PK, efficacy, anti-drug antibody against T-DXd <u>Other:</u> Biomarkers <u>Part 2:</u> <u>Primary:</u> Safety, tolerability, efficacy <u>Secondary:</u> PK, anti-drug antibody against T-DXd <u>Other:</u> Biomarkers	<u>DCO:</u> 01 Aug 2019 <u>Median treatment duration:</u> HER2-mutant NSCLC: 10.8 months (4.6-16.8) <u>Median duration of follow-up:</u> HER2-mutant NSCLC: 16.3 months (8.4-26.6)	<u>Part 1:</u> 27 <u>Part 2:</u> 265 Part 2a: 103 Part 2b: 41 Part 2c: 40 Part 2d: 60 (including 18 NSCLC subjects [11 with HER2-mutant NSCLC, 7 with HER2-expressing NSCLC]) Part 2e: 21	Advanced/ unresectable or metastatic cancer <u>Part 1:</u> BC, gastric or GEJ cancer <u>Part 2:</u> Part 2a: HER2-overexpressing BC Part 2b: HER2-overexpressing gastric or GEJ cancer Part 2c: HER2-low BC Part 2d: HER2-expressing solid tumors other than BC or GC (including HER2-mutant NSCLC and HER2-expressing NSCLC) Part 2e: HER2-expressing BC	14 centers 2 countries

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
DS8201-A-U201 (Study U201, DESTINY-Breast01)	03248492	Phase 2, multicenter, open-label, multiple-dose, 2-part study	T-DXd IV infusion Q3W <u>Part 1:</u> 5.4, 6.4, and 7.4 mg/kg <u>Part 2:</u> 5.4 mg/kg	<u>Primary:</u> ORR by ICR <u>Secondary:</u> Efficacy: investigator-assessed ORR, DCR, clinical benefit rate, DoR, best percent change in SoD of measurable tumors per RECIST v1.1 per ICR, PFS, OS <u>Other:</u> PK, safety	DCO: 08 Jun 2020 <u>Median treatment duration:</u> ^b 7.0 months (0.7-16.2) <u>Median duration of follow-up:</u> ^b 7.8 months (0.7-17.2)	Part 1: 119 Part 2: 134 Overall: 253	Subjects with HER2-positive unresectable or metastatic BC previously treated with trastuzumab emtansine	72 centers 8 countries

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
DS8201-A-J202 (Study J202, DESTINY-Gastric01)	03329690	Phase 2, multicenter, open-label, 3-cohort study (1 primary cohort and 2 exploratory cohorts). The primary cohort was randomized (2:1 ratio: T-DXd : TPC)	<u>Primary Cohort:</u> T-DXd 6.4 mg/kg as an IV infusion Q3W OR (2:1) TPC: Irinotecan monotherapy (IV infusion biweekly; starting dose of 150 mg/m ²) or Paclitaxel monotherapy (IV infusion weekly; starting dose of 80 mg/m ²)	<u>Efficacy endpoints:</u> ORR, OS, PFS, DoR, DCR, TTF, duration of SD, time to response, best percent change from baseline in SoD of measurable tumors, time to ECOG PS score to ≥2. <u>Other:</u> PK, safety	DCO: 03 Jun 2020 <u>Median duration of treatment:</u> T-DXd arm: 4.6 months (0.7-22.3) TPC arm: 2.8 months (0.5-13.1) <u>Median duration of follow-up:</u> Not available.	Primary Cohort: 188 T-DXd: 126 TPC: 62 (irinotecan: 55, paclitaxel: 7) Exploratory C1: 21 Exploratory C2: 24	Advanced HER2-expressing gastric or gastroesophageal adenocarcinoma, progressed on 2 prior regimens including a fluoropyrimidine agent and a platinum agent Primary Cohort: HER2-positive (IHC 3+ or IHC 2+/ISH positive) and prior trastuzumab	66 centers 2 countries

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-021)

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
DS8201-A-U206 (Study U206, DESTINY-Lung02)	04644237	Phase 2, multicenter, randomized	T-DXd IV infusion Q3W 5.4 or 6.4 mg/kg	<u>Primary:</u> ORR based on blinded ICR <u>Secondary:</u> investigator-assessed ORR, DCR, DoR, PFS, OS, safety, PK, HRQoL <u>Other:</u> time to response, HRQoL, QoL, tolerability, biomarkers, overall impression of cancer symptoms/ change in condition, healthcare resource use	<u>DCO:</u> 27 Jul 2021 <u>Median duration of treatment:</u> Not available. <u>Median duration of follow-up:</u> 5.4 mg/kg: 2 months (0.0-3.9) 6.4 mg/kg: 1 month (0.5-3.7)	5.4 mg/kg: 19 6.4 mg/kg: 9 Overall: 28	Subjects with metastatic NSCLC with a known activating HER2 mutation	20 centers 7 countries

^a Only data from subjects treated at T-DXd ≥5.4 mg/kg were used for pooled safety assessments.

The Applicant's Position:

This application is based primarily on the totality of efficacy and safety data from subjects in the target population of HER2-mutant NSCLC treated at the target dose of T-DXd (b) (4) from the Phase 2 Study U204 (Applicant - Table). Data from Phase 1 Study J101 support the evaluation.

Preliminary safety and PK data from the ongoing Phase 2 Study DS8201-A-U206 (DESTINY-Lung02) in which subjects with metastatic HER2-mutant NSCLC are randomized to T-DXd 5.4 mg/kg or T-DXd 6.4 mg/kg are also provided to support the application. The interim analysis results will be submitted in June 2022.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-021)

Enhertu[®] (fam-trastuzumab deruxtecan-nxki)The FDA's Assessment:

FDA disagrees with the applicant's original position. Results from Study U206 submitted during the review support a recommended dose of 5.4 mg/kg every 3 weeks. Based on this recommended dose, the primary efficacy and safety populations included patients treated at the 5.4 mg/kg dose level in Study U206. The results of Study U204 and Study J101 were considered supportive for this review.

8 STATISTICAL AND CLINICAL EVALUATION

8.1 REVIEW OF RELEVANT INDIVIDUAL TRIALS USED TO SUPPORT EFFICACY

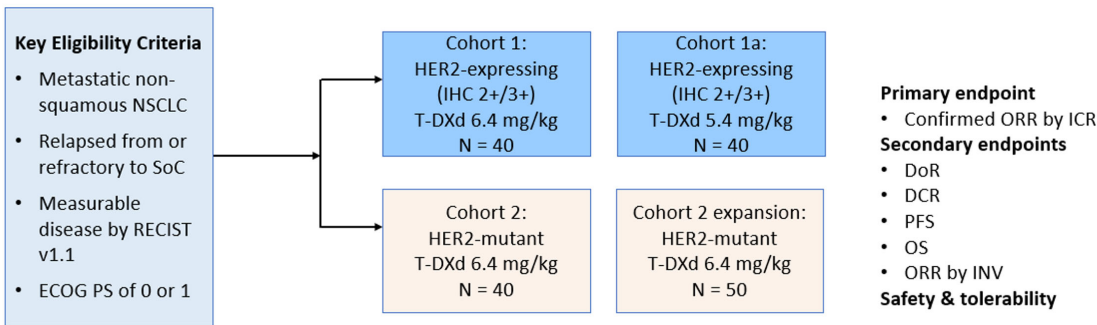
8.1.1 Study DS8201-A-U204 (DESTINY-Lung01)

Trial Design

The Applicant’s Description:

Basic Study Design: A Phase 2 multicenter, open-label, 2-cohort study in subjects with unresectable and/or metastatic HER2-overexpressing (defined as immunohistochemistry [IHC] 3+ or IHC 2+, determined prospectively by central testing) or HER2-mutant NSCLC (determined by local testing) (see **Applicant - Figure 5**).

Applicant - Figure 5: Study U204 (DESTINY-Lung01) Design



Trial Location: The study was conducted at sites in Japan, the U.S., and Europe. *Choice of Control Group:* There was no control group.

Diagnostic Criteria: Eligibility criteria selected subjects likely to benefit from treatment with T-DXd and were consistent with the patient population intended for treatment in the proposed indication.

Key inclusion criteria were:

- Age ≥20 years in Japan, ≥18 years in other countries.
- Pathologically documented unresectable and/or metastatic nonsquamous NSCLC.
- Tumors relapsed from or refractory to standard treatment or for which no standard treatment was available.
- Known documented activating HER2 mutation from an archival tumor tissue sample.
- Presence of at least 1 measurable lesion as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
Adequate organ function within 14 days before enrollment.

Key exclusion criteria were:

Prior treatment with HER2-targeted therapies, except for pan-HER class tyrosine kinase inhibitors.

Uncontrolled or significant cardiovascular disease.

History of noninfectious ILD/pneumonitis that required steroids, current ILD, suspected ILD/pneumonitis that could not be ruled out by imaging at Screening.

Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases could be included in the study. Subjects with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks had to have elapsed between the end of whole brain radiotherapy and study enrollment.

Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder, and any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement, or prior pneumectomy.

Dose Selection: Given the constraints in the early drug development program (e.g., drug supply) and the rare patient population, the initial clinical development plan in metastatic HER2-mutant NSCLC in Studies J101 and U204 took forward only 1 dose of T-DXd, the 6.4 mg/kg dose, to maximize the efficacy benefit in these patients and to quantify the effect of T-DXd in a greater number of subjects at a single dose. The protocol was subsequently amended (Protocol Version 6.0 dated 21 Feb 2020) to add a cohort of subjects with HER2-overexpressing NSCLC (Cohort 1a) to evaluate a 5.4 mg/kg dose in this population for further understanding of safety and efficacy of T-DXd at this dose.

Study Treatments: Subjects were assigned to 1 of the 3 cohorts and treated with T-DXd at 5.4 or 6.4 mg/kg as intravenous (IV) infusion Q3W.

Assignment to Treatment: There was no randomization. Eligible subjects were enrolled and assigned to treatment. Enrollment into Cohort 1a started after enrollment into Cohort 1 was complete.

Blinding: This was an open-label study.

Dose Modification/Dose Discontinuation: Specific management guidelines for dose modifications during the treatment period were provided in the protocol. Guidelines were applicable only to specific TEAEs (LVEF, electrocardiogram QT prolonged, troponin, hematologic toxicities, hepatic toxicity, infusion reaction, pulmonary toxicity, ocular toxicity, GI toxicity, blood creatinine increased, and other Grade 3 or 4 non-laboratory TEAEs) that were assessed as related to T-DXd by the investigator. For non-T-DXd

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related TEAEs, standard clinical practice was followed.

Administrative Structure: Responsibility for the conduct of the study was shared between the Applicant and contract research organizations. An independent ILD AC established for the T-DXd program was responsible for reviewing all cases of potential ILD/pneumonitis.

Procedure and Schedule: Screening tests were performed within 28 days prior to treatment start. During the treatment period, scheduled study visits were based on a 21-day (3-week) cycle and all subjects were assessed for disease progression every 6 weeks and at the end of treatment. The number of treatment cycles was not fixed and subjects continued treatment until the occurrence of any of the events that lead to study drug discontinuation. Regardless of reason for discontinuation from T-DXd, follow-up assessments were performed 40 days after the last study drug administration or before starting new anti-cancer treatment, whichever came first. Subsequently, long-term follow-up for survival was conducted every 3 months until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurred first.

Concurrent Medications: During the treatment period, prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days were permitted. Hematopoietic growth factors could be used for prophylaxis or treatment based on the clinical judgment of the investigator. Prophylactic or supportive treatment of study-drug induced AEs were otherwise to be as per investigator's discretion and institutional guidelines. Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments was discouraged, but not prohibited.

Treatment Compliance: As T-DXd was administered IV under the supervision of clinical study personnel at the study site, compliance was ensured if subject attended scheduled visits.

Rescue Medication: Rescue medications were not planned in Study U204.

Subject Completion, Discontinuation, or Withdrawal: The study treatment continued according to dosing criteria in the absence of progressive disease (PD) (per RECIST v1.1 or clinical progression), AE, death, pregnancy, protocol deviation, withdrawal of consent by subject, lost to follow-up, physician decision, study termination, or other reasons. If the study treatment was delayed more than 28 days from the planned date of administration, the subject was withdrawn from treatment, but was followed for survival unless prohibited by local laws.

Study Endpoints

The Applicant's Description:

Primary Efficacy Endpoint:

The primary endpoint was ORR assessed by ICR. The ORR was defined as the proportion of subjects who

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achieved a best overall response of complete response (CR) or partial response (PR), as defined by RECIST v1.1. Confirmation of CR/PR was required for this study.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints included DoR (by ICR and investigator assessment), disease control rate (DCR) (by ICR and investigator assessment), PFS (by ICR and investigator assessment), ORR (by investigator assessment), and OS.

Exploratory Efficacy Endpoints:

Exploratory efficacy endpoints included time to response (by ICR and investigator assessment), best percent change from baseline in the SoD of measurable tumors (by ICR and investigator assessment).

Other Endpoints:

Other endpoints included PK, immunogenicity, and safety.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study design and efficacy endpoints for Study U204, which are consistent with the study protocol.

As the primary efficacy and safety populations were derived from Study U206 (DESTINY-Lung02), details of this study are described below.

Study DS8201-A-U206 (DESTINY-Lung02)

Trial Design

Basic Study Design: A randomized, multicenter, two-arm study in patients with *HER2*-mutant NSCLC who had disease recurrence or progression during or after at least one prior anticancer therapy in the metastatic or locally advanced setting, including platinum chemotherapy. Randomization was stratified by prior anti-PD-(L)1 treatment.

Trial Location: The study was conducted at sites in North America, Europe, and Asia-Pacific.

Choice of Control Group: There was no control group.

Diagnostic Criteria: The eligibility criteria selected for patients likely to benefit from treatment with T-DXd (5.4 mg/kg or 6.4 mg/kg) and were consistent with the patient population intended for treatment in the proposed indication.

Key inclusion criteria were:

Age ≥18 years.

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Pathologically documented unresectable and/or metastatic nonsquamous NSCLC.

Patients who had previous treatment, including platinum chemotherapy, in the metastatic or locally advanced setting not amenable to curative surgery or radiation.

Must have progressed during or after the last treatment regimen or discontinued because of unacceptable toxicity.

Known documented activating *HER2* mutation from an archival tumor tissue sample.

Presence of at least 1 measurable lesion as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

Adequate organ function within 14 days before enrollment.

Left ventricular ejection fraction (LVEF) $\geq$ 50% within 28 days before randomization.

Key exclusion criteria were:

Had a known driver mutation or genomic alteration in EGFR, BRAF, MET, ALK, ROS1, RET, or NTRK.

Uncontrolled or significant cardiovascular disease.

History of noninfectious ILD/pneumonitis that required steroids, current ILD, or suspected ILD/pneumonitis that could not be ruled out by imaging at Screening. Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Patients with clinically inactive brain metastases could be included in the study. Patients with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks had to have elapsed between the end of whole brain radiotherapy and study enrollment.

Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder, and any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement, or prior pneumectomy.

Dose Selection: Both 5.4 and 6.4 mg/kg doses of trastuzumab deruxtecan have shown clinical efficacy in multiple cancer indications. Prior to this trial, the 5.4 mg/kg dose was not previously

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tested in patients with *HER2* mutated NSCLC. However, the 5.4 mg/kg dose had been evaluated in patients with *HER2*-expressing NSCLC.

Study Treatments: T-DXd was administered on Day 1 of every 3 weeks (Q3W) at a dose of 5.4 mg/kg or 6.4 mg/kg as an intravenous (IV) infusion.

Assignment to Treatment: 150 patients were planned to be randomized in a 2:1 ratio to receive T-DXd at a dose of 5.4 mg/kg or 6.4 mg/kg, respectively.

Blinding: Per protocol, the study was blinded to patients, investigators, and study site personnel. The Applicant and the contract research organizations (CROs) were not blinded to the treatment assignment.

Dose Modification/Dose Discontinuation: Specific management guidelines for dose modifications during the treatment period were provided in the protocol. Specific guidelines were provided for cardiac, hepatic, hematologic, and non-hematologic (including ILD/pneumonitis) toxicities.

Administrative Structure: Responsibility for the conduct of the study was shared between the Applicant and CROs. An independent ILD adjudication committee (AC) established for the T-DXd program was responsible for reviewing all cases of potential ILD/pneumonitis.

Procedure and Schedule: Screening tests were performed within 28 days prior to starting treatment. During the treatment period, scheduled study visits were based on a 21-day (3-week) cycle and all patients were assessed for disease progression every 6 weeks and at the end of treatment. The number of treatment cycles was not fixed and patients continued treatment until the occurrence of any of the events that lead to study drug discontinuation. Regardless of the reason for discontinuation from T-DXd, follow-up assessments were performed 40 days after the last study drug administration or before starting new anti-cancer treatment, whichever came first. Subsequently, long-term follow-up for survival was conducted every 3 months until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurred first.

Concurrent Medications: During the treatment period, prophylactic antiemetic agents prior to infusion of T-DXd and on subsequent days were permitted. Hematopoietic growth factors could be used for prophylaxis or treatment based on the clinical judgment of the investigator. Prophylactic or supportive treatment of study-drug induced adverse events (AEs) were otherwise per investigator's discretion and institutional guidelines. Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments was discouraged, but not prohibited.

Treatment Compliance: As T-DXd was administered IV under the supervision of clinical study personnel at the study site, compliance was ensured if the patients attended scheduled visits.

Rescue Medication: Not applicable.

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Patient Completion, Discontinuation, or Withdrawal: The study treatment continued according to dosing criteria in the absence of progressive disease (PD) (per RECIST v1.1 or clinical progression), AE, death, pregnancy, protocol deviation, withdrawal of consent by the patient, lost to follow-up, physician decision, study termination, or other reasons. If the study treatment was delayed more than 28 days from the planned date of administration, the patient was withdrawn from treatment, but was followed for survival unless prohibited by local laws.

Study Endpoints

Primary Efficacy Endpoint:

The primary endpoint was ORR assessed by BICR. The ORR was defined as the proportion of patients whose tumors shrank to meet the requirements of an overall response of complete response (CR) or partial response (PR), as defined by RECIST v1.1. Confirmation of response was required for this study.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints included ORR (by investigator assessment), DoR (by BICR and investigator assessment), disease control rate (DCR) (by BICR and investigator assessment), PFS (by BICR and investigator assessment), and OS. PFS and OS were not reported in the interim analysis.

Exploratory Efficacy Endpoints:

Exploratory efficacy endpoints included time to response (by BICR and investigator assessment), best percent change from baseline in the sum of diameters (SoD) of measurable tumors (by BICR and investigator assessment).

Other Endpoints:

Other endpoints included safety, PK, immunogenicity, and patient-reported outcome (PRO) endpoints (not reported in the interim analysis).

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical analysis plan was finalized prior to the database lock. The primary analysis was conducted as of the data cut-off (DCO) date of 03 May 2021 after ensuring a minimum follow-up of 6 months after onset of response in Cohort 2 subjects to allow adequate assessment of ORR and durability of response.

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The Full Analysis Set (FAS) included all subjects who signed the main informed consent form and enrolled in the study and was the primary analysis set for all efficacy analyses. Following the intent-to-treat principle, subjects were analyzed according to the cohort they were assigned to at enrollment. The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug. Subjects were analyzed according to the treatment (dose level) received. Treatment (dose level) received was the planned treatment (dose level) for the cohort which the subject was assigned to at enrollment unless the planned treatment (dose level) for another cohort, for which the subject would also have been eligible for enrollment, was received throughout the study.

The primary efficacy analysis was based on ICR of tumor scans. Best overall response was defined as the best response among all overall responses recorded from the start of treatment until PD/death or the start of a new anticancer therapy, whichever occurred earlier. The point estimate of ORR and its 2-sided exact 95% CI using Clopper-Pearson method were calculated. A sensitivity analysis of the primary efficacy endpoint was performed in the Response-evaluable Set, which included all enrolled subjects who received ≥ 1 dose of study drug and had measurable disease at Baseline per ICR, using the same analyses as described from the primary efficacy endpoint.

Distribution of time to event endpoints (DoR, PFS, OS) was estimated using Kaplan-Meier methods. For the ORR based on investigator assessment, same analyses as described from the primary efficacy endpoint were done. Time to response was summarized descriptively. Best percent change from baseline in the SoD of target lesions was plotted.

Subgroup analyses of ORR based on ICR by prespecified subgroups were conducted.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the statistical analysis plan for Study U204. For efficacy analyses in non-comparative trials, FDA recommends that the as-treated population (same as the Safety Analysis Set described above), which includes all patients who received at least one dose of study drug, be the primary analysis population. Given that all patients in the Full Analysis Set were treated, it is considered the same as the as-treated population. FDA notes that time-to-event endpoints such as PFS and OS are not interpretable and are considered descriptive only in non-comparative trials.

The statistical analysis plan (SAP) for Study U206 is described below.

The SAP Version 1.0 was finalized on February 17, 2022. There have been no SAP amendments to FDA's knowledge since the finalization of the initial SAP. An ad-hoc interim analysis (IA) was conducted as of the data cut-off (DCO) date of July 27, 2021 for early assessment of efficacy and safety. The purpose of this analysis was to provide additional data (on safety, PK, and change in sum of target lesions) in support of the regulatory review for the *HER2*-mutant NSCLC sBLA. Approximately 25 patients were expected to be randomized and dosed by the DCO. Two IAs

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were planned for this study. The first IA was expected to occur when at least 75 patients received a dose of study drug (5.4 mg/kg or 6.4 mg/kg) and had at least 4.5 months of follow-up or discontinued treatment. This prespecified early cohort allowed for patients on study to have 3 imaging assessments. The second IA was expected to occur approximately 6 months after the first IA. The final analysis was expected to occur when all patients have completed at least 9 months of follow-up after at least one CT scan post-baseline or after discontinuing treatment. The second IA may not be performed if it is anticipated to fall within 3 months of the final analysis and the data are sufficiently mature.

The Applicant submitted results from the first IA during the review cycle (DCO date: March 24, 2022). At FDA's request, the Applicant updated efficacy results (specifically ORR and DOR) for patients treated with T-DXd 5.4 mg/kg in the prespecified early cohort (patients with at least 4.5 months follow-up as of the March 24, 2022 DCO). This provided an additional 90-days follow-up with a DCO date of June 22, 2022 and was used for the primary efficacy evaluation. All efficacy analyses were performed on the full analysis set (FAS) and the prespecified early cohort. However, FDA considers the prespecified early cohort as the primary efficacy population to allow for a more precise estimation of treatment benefit. The FAS consists of all randomized patients. The prespecified early cohort is a subset of FAS patients who had at least 4.5 months of follow-up. Safety analyses were performed using the safety analysis set. The Safety Analysis Set is a subset of FAS patients who received at least one dose of study drug.

In this study, each dose level was evaluated separately. The ORR and its exact 95% confidence interval (CI) were estimated using the Clopper-Pearson method. The median DOR was summarized using the Kaplan-Meier method and its 95% CI using the Brookmeyer-Crowley method. The primary analysis of ORR by BICR was also performed for exploratory purposes by prespecified subgroups if at least 10 patients in each group were available.

The sample size for each dose level (100 patients at 5.4 mg/kg and 50 patients at 6.4 mg/kg) was calculated to achieve an adequate precision to exclude a clinically relevant ORR of 26.4% based on the 2-sided exact 95% CI using Clopper-Pearson method.

Protocol Amendments

The Applicant's Description:

The initial study protocol, dated 13 Nov 2017, was amended 6 times, 2 times prior to first subject enrolled and 4 times subsequently. Amendments that affected the planned analyses are summarized below.

Amendment 3 added an interim analysis for efficacy and safety.

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Amendment 4 added a second interim analysis for safety, increased Cohort 2 enrollment from 40 to 90 subjects, and provided rationale for Cohort 2 expansion and updated planned sample size calculations.

Amendment 5 added Cohort 1a to the study and a third interim analysis.

The changes did not impact the integrity of the trial or the interpretation of the results.

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments for Study U204. The Amendment 3 (Protocol Version 4.0) also updated the definitions of the efficacy analysis populations to align with the intent-to-treat principle.

The Protocol Version 1.0 for Study U206, dated June 2, 2020, was amended twice. Protocol amendments that affected the planned analyses are summarized below.

Amendment 1 (Version 2.0, dated October 22, 2020) changed the randomization allocation ratio of the 5.4 mg/kg and 6.4 mg/kg doses from 1:1 to 2:1, and increased the sample size from 100 to 150 patients.

Amendment 2 (Version 3.0, dated December 1, 2021) added two interim analyses for efficacy and safety of two doses.

The changes did not impact the integrity of the trial or the interpretation of the results.

8.1.2 Study DS8201-A-J101 (Supportive Study)

Trial Design

The Applicant's Description:

A Phase 1, 2-part, multicenter, nonrandomized, open-label, multiple-dose, first-in-human study of T-DXd, with study sites in Japan and the U.S. Part 1 (Dose Escalation) was to identify the maximum tolerated dose (MTD) or the recommended Phase 2 dose of T-DXd and evaluated doses ranging from 0.8 mg/kg to 8.0 mg/kg. Part 2 (Dose Expansion) was to further assess the safety, tolerability, and efficacy of T-DXd at the MTD/recommended Phase 2 doses of 5.4 mg/kg and 6.4 mg/kg. Dose Expansion was conducted in 5 cohorts of subjects with various tumor types (BC, gastric or GEJ adenocarcinoma) and levels of HER2 expression (**Applicant - Figure 6**). The target population of subjects with metastatic NSCLC was enrolled in Part 2d, with 11 HER2-mutant NSCLC subjects and 7 HER2-expressing NSCLC subjects.

Key criteria for enrollment in Part 2d of the dose expansion phase, subjects had to have:

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An ECOG PS of 0 or 1.

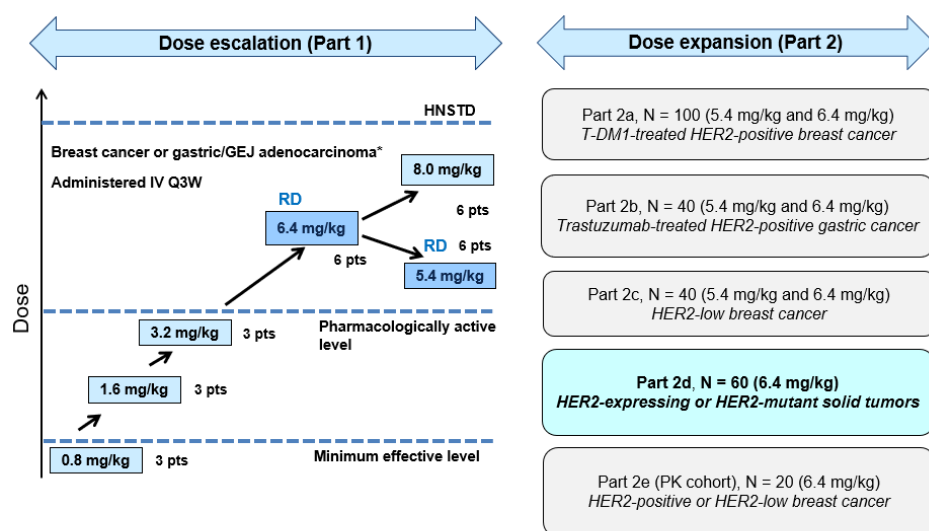
Pathologically documented advanced/unresectable or metastatic solid malignant tumor (other than BC, gastric or GEJ adenocarcinoma) with either HER2 expression or with HER2 mutation (determined by next generation sequencing or other analysis techniques as appropriate) that was refractory to standard treatment, or with intolerance to standard treatment, or for which no standard treatment was available.

Measurable disease based on RECIST v1.1.

Unlike Study U204, HER2 expression status was based on local laboratory reports of archival tissue samples. Otherwise, eligibility criteria, study treatments, dose modifications, schedule of events, and overall study conduct were similar between the 2 studies. Similar to Study U204, ORR assessed by ICR and based on RECIST v1.1 was the primary endpoint.

Data for this study had a clinical DCO date of 01 Aug 2019.

Applicant - Figure 6: Study J101 Design



- HER2 status was assessed on archival tissue in both Parts 1 and 2

Study Endpoints

Efficacy endpoints included ORR, OS, DCR, DoR, and PFS. Except for OS, efficacy endpoints were assessed by both the investigator and ICR. OS was added as an efficacy endpoint in Version 10.0 of the protocol (dated 14 Sep 2017) after follow-up procedures were changed to add follow-up for survival status until death or the DCO date.

The FDA's Assessment:

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FDA agrees with the Applicant's description of Study J101.

8.1.3 Study Results – Study U204

Compliance with Good Clinical Practice

The Applicant's Position:

Study U204 was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

The FDA's Assessment:

FDA agrees with the Applicant's position. Study U206 was also reported to be conducted in compliance with Good Clinical Practice.

Financial Disclosure

Applicant's Description of the Data:

Financial disclosure information was provided for clinical investigators involved in the covered clinical Study U204. The summary of financial disclosure information is provided in Appendix 19.2. There was 1 clinical investigator with disclosable financial interests or agreements under the significant payments of other sorts of financial disclosure category.

The Applicant's Position:

No concerns were raised regarding the overall integrity of the study data.

The FDA's Assessment:

FDA agrees with the Applicant's position. No concerns were raised regarding the overall integrity of the study data.

Patient Disposition

The Applicant's Description of the Data:

A total of 91 NSCLC subjects with HER2 mutation were enrolled in Study U204 and were included in the FAS.

The median duration of study follow-up in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204 was 13.1 months (range: 0.7 to 29.1). Fifteen (16.5%) subjects were ongoing on treatment with T-DXd 6.4 mg/kg and 76 (83.5%) subjects had discontinued study drug, with PD (37.4%) and AEs (29.7%) being the 2 most common reasons for discontinuation.

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The Applicant's Position:

The most common reason for study drug discontinuation was PD as expected for the population studied.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition for Study U204. Patient disposition for Study U206 is described below. Data from the March 24, 2022 DCO are presented for purposes of comparison between arms and data from the June 22, 2022 DCO are presented for extended follow-up.

March 24, 2022 DCO

As of the DCO of March 24, 2022, a total of 152 patients with NSCLC with *HER2* mutations were randomized in Study U206 and 151 of them were treated with T-DXd. Among those, 80 patients were included in the prespecified early cohort. This included 52 patients in the 5.4 mg/kg arm and 28 patients in the 6.4 mg/kg arm. One patient in the 5.4 mg/kg arm of the prespecified early cohort was not treated due to a COVID-19 infection.

As of the DCO of March 24, 2022, the median duration of study follow-up in patients in the T-DXd 5.4 mg/kg arm in the prespecified early cohort of Study U206 was 5.6 months (range: 1.1 to 11.7). Twenty-six (51%) patients were continuing to receive treatment with T-DXd 5.4 mg/kg and 25 (49%) patients had discontinued the study drug, with PD (31%) and AEs (16%) being the two most common reasons for discontinuation.

As of the DCO of March 24, 2022, the median duration of study follow-up in patients in the T-DXd 6.4 mg/kg arm in the prespecified early cohort of Study U206 was 5.4 months (range: 0.6 to 12.1). Thirteen (46%) patients were continuing to receive treatment with T-DXd 6.4 mg/kg and 15 (54%) patients had discontinued the study drug, with PD (25%) and AEs (18%) being the two most common reasons for discontinuation.

June 22, 2022 DCO

At the time of the efficacy update (DCO June 22, 2022), the median duration of study follow-up in patients in the T-DXd 5.4 mg/kg arm in the prespecified early cohort of Study U206 was 8.0 months (range: 1.1 to 14.6). Twenty-two (43%) patients were continuing to receive treatment with T-DXd 5.4 mg/kg and 29 (57%) patients had discontinued the study drug, with PD (39%) and AEs (16%) being the two most common reasons for discontinuation.

As described above, the most common reason for study drug discontinuation in Study U206 was progressive disease.

Protocol Violations/Deviations

Applicant's Description of the Data:

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A total of 26 (28.6%) subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204 met 1 or more of the criteria for major protocol deviations. The most frequent major protocol deviations were related to visit/procedure required (11 [12.1%] subjects), followed by non-compliance (9 [9.9%] subjects). Major protocol deviations related to visit/procedure were largely driven by safety laboratory assessments that were not done at certain weeks, which was unrelated to the coronavirus disease-2019 pandemic in all but 1 subject. Major protocol deviations related to non-compliance were mostly SAE/ILD events not reported within the correct timeframe (mostly by mistake and in 2 subjects because of lack of staff during the coronavirus disease-2019 pandemic). Two subjects continued receiving T-DXd despite meeting criteria for T-DXd discontinuation.

The Applicant's Position:

The impact of any individual missing data points is considered to be minimal because each of the safety laboratory assessments were repeated multiple times throughout the study. The major protocol deviations were considered to be unlikely to have a meaningful impact on integrity of the study including study conduct, subject safety, or the overall conclusions of the study.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition for Study U204. Patient disposition for Study U206 is described below.

A total of 8 (15%) patients treated with T-DXd 5.4 mg/kg in Study U206 met one or more of the criteria for major protocol deviations. The most frequent major protocol deviations were related to serious adverse events not reported within a 24-hour timeline (6 [12%] patients), followed by patients not meeting inclusion criteria but enrolled in the study (2 [3.8%] patients), and informed consent not obtained prior to any study procedures being performed (2 [3.8%] patients).

A total of 4 (14%) patients treated with T-DXd 6.4 mg/kg in Study U206 met one or more of the criteria for major protocol deviations. The most frequent major protocol deviations were related to serious adverse events not reported within a 24-hour timeline (3 [11%] patients), followed by patients not meeting inclusion criteria but enrolled in the study (2 [7%] patients).

Given the described low prevalence, the impact of protocol deviations for Study U206 is likely to be minimal.

Table of Demographic Characteristics

Applicant's Presentation of the Data:

Key demographic characteristics of subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study U204 are summarized in **Applicant - Table 7**.

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Applicant - Table 7: Demographic and Baseline Disease Characteristics (FAS)

Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 11)
Age (years)		
n	91	11
Mean (SD)	60.3 (11.94)	57.1 (17.81)
Median (min, max)	60.0 (29, 88)	58.0 (23, 83)
Sex (n [%])		
Male	31 (34.1)	3 (27.3)
Female	60 (65.9)	8 (72.7)
Region (n [%])		
Asia	23 (25.3)	3 (27.3)
North America	35 (38.5)	8 (72.7)
Europe	33 (36.3)	0
Number of lines of prior systemic therapy for advanced/metastatic disease (n [%])		
≤2	61 (67.0)	2 (18.2)
>2	30 (33.0)	9 (81.8)
Prior treatment with anti-PD-1/PD-L1 inhibitor (n [%])		
Yes	60 (65.9)	8 (72.7)
No	31 (34.1)	3 (27.3)
Prior treatment with platinum therapy (n [%])		
Yes	86 (94.5)	11 (100.0)
No	5 (5.5)	0
Prior treatment with platinum therapy and an anti-PD-1/PD-L1 inhibitor in combination (n [%])		
Yes	30 (33.0)	0
No	61 (67.0)	11 (100.0)
Prior treatment with platinum therapy and an anti-PD-1/PD-L1 inhibitor but not in combination (n [%])		
Yes	27 (29.7)	8 (72.7)
No	64 (70.3)	3 (27.3)
CNS metastasis at Baseline (n [%]) ^a		

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 11)
Yes	33 (36.3)	2 (18.2)
No	58 (63.7)	9 (81.8)
Smoking status (n [%])		
Never	52 (57.1)	0
Previous	37 (40.7)	0
Current	2 (2.2)	0
Missing/unknown/not reported	0	11 (100.0)

^a CNS metastases include brain metastases or spinal cord metastases.

DCO date: 03 May 2021 for Study U204 and 01 Aug 2019 for Study J101. Program: t-dm.sas. Source data: ADSL

The Applicant's Position:

Demographic characteristics were generally consistent with the broader population of patients with HER2-mutant advanced NSCLC seen in clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's description of the demographic and baseline characteristics in Study U204. Demographic and baseline characteristics for Study U206 are described below (Table 8).

Table 8: Demographic and Baseline Disease Characteristics (Prespecified Early Cohort), Study U206

Parameter	T-DXd 5.4 mg/kg (N = 52)	T-DXd 6.4 mg/kg (N = 28)
Age (years)		
Median	57.5	64.0
Min, max	30, 78	27, 81
≥65	21 (40)	11 (39)
Female (n [%])	36 (69)	17 (61)
Race (n [%])		
Asian	41 (79)	21 (75)
Black or African American	0	1 (3.6)
White	6 (12)	1 (3.6)

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Parameter	T-DXd 5.4 mg/kg (N = 52)	T-DXd 6.4 mg/kg (N = 28)
Other	5 (10)	5 (18)
Region (n [%])		
Asia	40 (77)	21 (75)
North America	3 (6)	1 (3.6)
Europe	7 (14)	6 (21)
Australia	2 (3.9)	0
Number of lines of prior systemic therapy for advanced/metastatic disease (n [%])		
≤2	32 (62)	14 (50)
>2	20 (39)	14 (50)
Prior treatment with anti-PD-1/PD-L1 inhibitor (n [%])		
Yes	38 (73)	20 (71)
ECOG at baseline (n [%])		
0	15 (29)	11 (39)
1	37 (71)	17 (61)
Type of HER2 mutation (n [%])		
Kinase	49 (94)	28 (100)
Extracellular	3 (6)	0
CNS metastasis at Baseline (n [%])		
Yes	17 (33)	12 (43)
Smoking status (n [%])		
Never	26 (50)	12 (43)
Former	26 (50)	16 (57)

DCO: March 24, 2022

Source: FDA Reviewer – generated analyses based on Applicant submitted data

Demographic characteristics in Study U206 were generally consistent with the broader population of patients with *HER2*-mutant advanced NSCLC seen in clinical practice with the exception that an increased proportion of foreign patients were included in Study U206 compared to Study U204. Together with the experience with T-DXd in U.S. patients in Study U204, results from Study U206 appear to be applicable to U.S. patients.

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Applicant's Presentation of Data:

Key baseline characteristics of subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study U204 are summarized in **Applicant - Table 7**.

The Applicant's Position:

Key baseline characteristics were generally consistent with the broader population of patients with HER2-mutant advanced NSCLC seen in clinical practice.

Treatment Compliance, Concomitant Medications

The median relative dose intensity (i.e., percentage of intended dose administered) was 90.5% (range: 64.4% to 102.4%). All subjects received concomitant medications. There were no major protocol deviations due to the use of prohibited medications.

The Applicant's Position:

Treatment compliance indicated that T-DXd regimen was tolerable by most subjects.

The FDA's Assessment:

FDA agrees with the Applicant's results of other baseline and disease characteristics in Study U204. Other baseline and disease characteristics for Study U206 are described in the table above (Table 8). The median relative dose intensity (i.e., percentage of intended dose administered) for T-DXd 5.4 mg/kg in Study U206 at the March 24, 2022 DCO was 97% (range: 68% to 107%). All patients received concomitant medications. There were no major protocol deviations due to the use of prohibited medications.

This high treatment compliance indicated that T-DXd 5.4 mg/kg was tolerated by most patients in Study U206.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Applicant's Presentation of Data:

Objective Response Rate

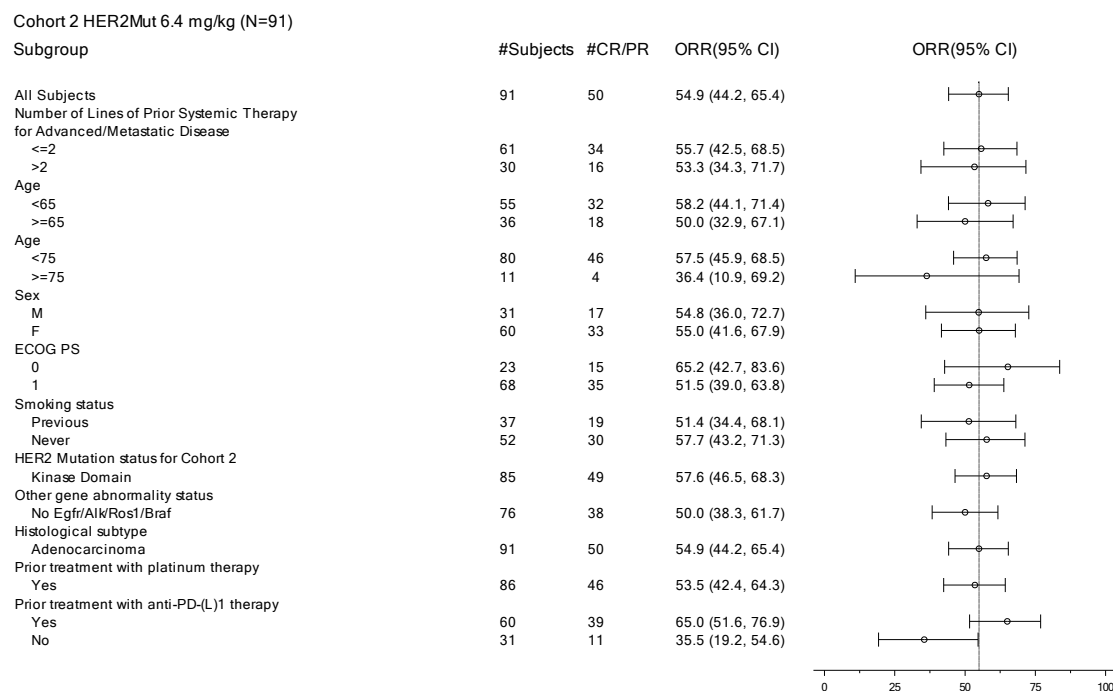
In subjects with HER2 mutation treated with T-DXd 6.4 mg/kg, ORR based on ICR was 54.9%, with 1 (1.1%) subject achieving confirmed CR and 49 (53.8%) achieving confirmed PR (**Applicant - Table 11**). Sensitivity analysis of ORR based on ICR in the Response-evaluable Set (56.2% [95% CI: 45.3, 66.7]) were consistent with those from the FAS.

Subgroup Analyses of Objective Response Rate

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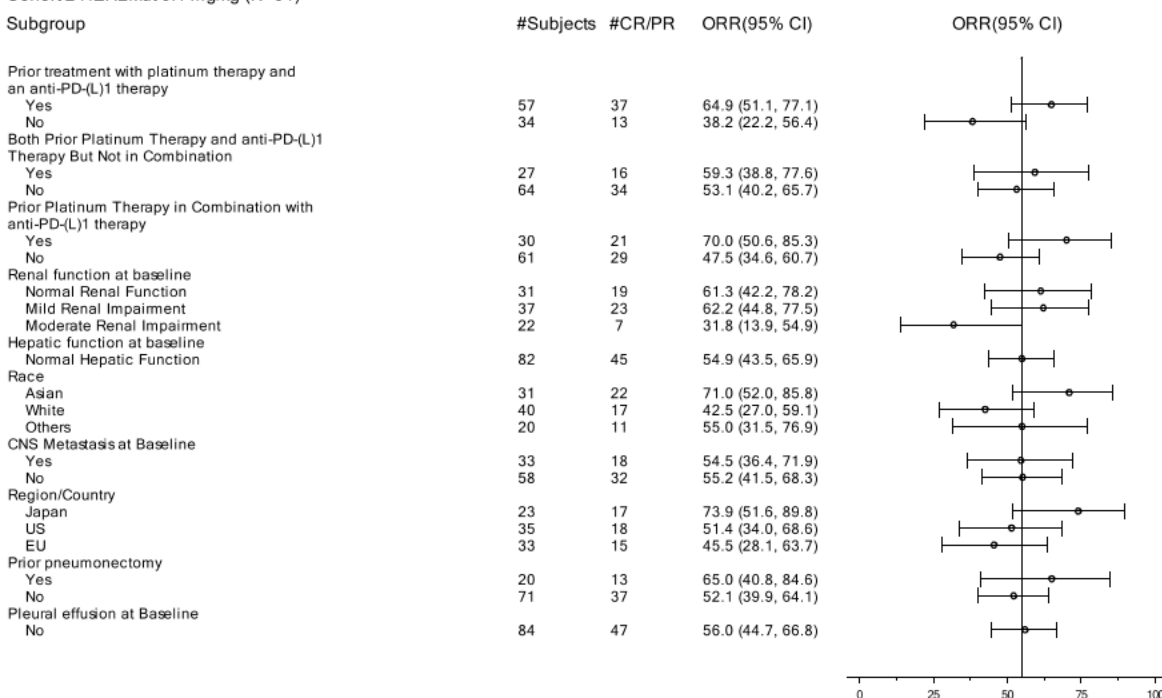
Subgroup analyses of ORR were consistent across key prespecified subgroups (**Applicant - Figure 7**). With respect to prior therapy, ORR was 53.5% (95% CI: 42.4, 64.3) in subjects with prior platinum-based therapy, 64.9% (95% CI: 51.1, 77.1) in subjects with both prior platinum-based therapy and anti-PD-1/PD-L1 therapy regardless of in combination or sequentially, 70.0% (95% CI: 50.6, 85.3) in subjects with prior platinum-based therapy in combination with anti-PD-1/PD-L1 therapy, and 59.3% (95% CI: 38.8, 77.6) in subjects with prior platinum-based therapy and anti-PD-1/PD-L1 therapy but not in combination.

Applicant - Figure 7: ORR on ICR in HER2-mutant NSCLC by Subgroup (FAS)



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Cohort 2 HER2Mut 6.4 mg/kg (N=91)



The 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution.

The Applicant's Position:

T-DXd demonstrated strong and clinically meaningful improvement in ORR in subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study U204. Sensitivity analysis was consistent with the primary analysis. The ORR was consistent across prespecified subgroups.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description that the efficacy results from primary and subgroup analyses were generally consistent for Study U204. In a total of 91 patients treated with T-DXd 6.4 mg/kg, ORR per ICR was 55% (95% CI: 44, 65). The sensitivity analysis performed in the Response-Evaluable Set also showed consistent results with the primary analysis. FDA's efficacy evaluation is based on the magnitude of the observed ORR, durability of responses, and overall benefit-risk assessment.

Results for Study U206 are described below. Data from the March 24, 2022 DCO are presented for purposes of comparison between arms and data from the June 22, 2022 DCO are presented for extended follow-up.

Overall Response Rate (Study U206)

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March 24, 2022 DCO

As of the DCO of March 24, 2022, in patients treated with T-DXd 5.4 mg/kg in the prespecified early cohort, the ORR based on ICR was 54% (95% CI: 40, 68), with 1 (1.9%) patient having a confirmed CR and 27 (52%) having confirmed PR.

At this DCO, for patients treated with T-DXd 6.4 mg/kg in the prespecified early cohort, the ORR based on ICR was 43% (95% CI: 25, 63), with 1 (3.6%) patient having a confirmed CR and 11 (39%) having confirmed PR.

June 22, 2022 DCO

As of the DCO of June 22, 2022, in patients treated with T-DXd 5.4 mg/kg in the prespecified early cohort, the ORR based on ICR was 58% (95% CI: 43, 71), with 1 (1.9%) patient having a confirmed CR and 29 (56%) having confirmed PR (Table 9).

Table 9: ORR Per BIRC (T-DXd 5.4 mg/kg, Prespecified Early Cohort), Study U206, DCO June 22, 2022

Parameter	T-DXd 5.4 mg/kg (N=52)
Best overall response (confirmed), n (%)	
CR	1 (1.9)
PR	29 (56)
SD	17 (33)
PD	2 (3.9)
NE	3 (6)
Confirmed ORR	
n (%)	30 (58)
95% CI ^a	(43, 71)

^a Estimated using Clopper-Person exact confidence interval

DCO: June 22, 2022

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease;

NE – not evaluable

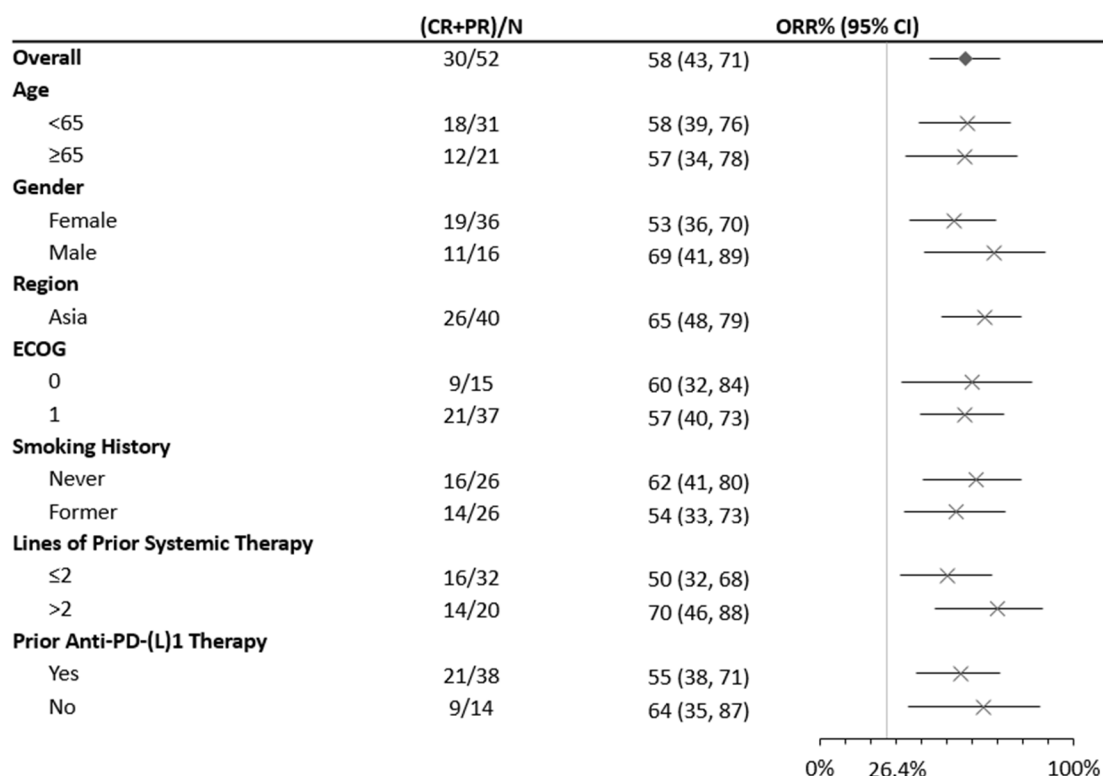
Source: FDA Reviewer – generated analyses based on Applicant submitted data

Subgroup Analyses of Objective Response Rate (Study U206)

Subgroup analyses of ORR in the prespecified early cohort treated with T-DXd 5.4 mg/kg were consistent across key prespecified subgroups (Figure 8).

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Figure 8: ORR Per BIRC by Subgroup (T-DXd 5.4 mg/kg, Prespecified Early Cohort), Study U206



The vertical line is the prespecified reference ORR to be excluded from the lower bound of 95% CI.

DCO: June 22, 2022

Source: FDA Reviewer – generated analyses based on Applicant submitted data

T-DXd at 5.4 mg/kg appears to be efficacious in patients with *HER2*-mutant NSCLC across subgroups. There have been a limited number of patients treated with T-DXd at 5.4 mg/kg with adequate follow-up (prespecified early cohort [N=52]). With that, subgroup analyses were performed only for categories that have at least 10 patients. (b) (4)

Data Quality and Integrity

Applicant's Presentation of Data:

A Risk-Based Quality Management approach was developed in Jun 2020. Quality tolerance limits (QTLs)

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were identified in Jun 2020 and monitored during the study. The critical data, critical processes, associated risks, and mitigation activities (including QTLs) were identified cross-functionally using empirical methods. During the conduct of the study, the identified risks were monitored and mitigated by a variety of central, remote, and onsite activities. Central monitoring outputs, including key risk indicators and QTLs, were reviewed regularly by the study team. No QTL deviation was identified as important during the on-treatment phase of the study.

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. These datasets were sufficiently complete to allow for a thorough review of efficacy. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant.

The FDA's Assessment:

FDA agrees that there were no major concerns in the data quality and integrity for Study U204. The data was sufficient to conduct the review. There were also no major concerns in the data quality and integrity for Study U206.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Presentation of Data:

Duration of Response

The median DoR based on ICR was 9.3 months (95% CI: 5.7, 14.7) in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204.

Disease Control Rate

The DCR based on ICR was 92.3% (95% CI: 84.8, 96.9) in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204.

Progression-free Survival

The median PFS based on ICR was 8.2 months (95% CI: 6.0, 11.9) in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204. A total of 35 (38.5%) subjects were censored for analysis. The most common reason for censoring was new anticancer therapy (15.4%).

Overall Survival

The median OS estimated by Kaplan-Meier methods was 17.8 months (95% CI: 13.8, 22.1) in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204, with OS events reported in 47 (51.6%) subjects. The estimated 6- and 12-month OS rates were 83.3% and 68.3%, respectively.

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The Applicant's Position:

The observed DoR, DCR, PFS, and OS in patients with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study U204 further support the clinically meaningful antitumor activity of T-DXd in this patient population.

The FDA's Assessment:

FDA agrees with the Applicant's results for secondary endpoints for Study U204. FDA notes that DCR is not considered to be a clinically relevant endpoint for efficacy evaluation. Time-to-event endpoints such as PFS and OS are not interpretable and are considered descriptive only in non-comparative trials. Results for secondary endpoints for patients in Study U206 treated at T-DXd 5.4 mg/kg are described below.

Efficacy Results – Secondary and other relevant endpoints (Study U206, 5.4mg/kg Arm)

Duration of Response

The median DoR based on ICR was 8.7 months (95% CI: 7.1, NE) in patients treated with T-DXd 5.4 mg/kg in the prespecified early cohort of Study U206 at the June 22, 2022 DCO (Table 10).

Table 10. DOR Per BIRC (Prespecified Early Cohort), Study U206, DCO June 22, 2022

Parameter	T-DXd 5.4 mg/kg (N=52)
Number of patients with confirmed CR/PR, n (%)	30
Number of events, n (%)	7 (23)
Number of censored, n (%)	23 (77)
Median (95% CI) ^a , months	8.7 (7.1, NE)
Range, months	1.3+, 12.5+
Patients with DoR >6 months ^b , n (%)	10 (33)

NE: not estimable, +: ongoing response

^a Estimated using Kaplan-Meier method

^b Based on the observed number of patients with a response lasting > 6 months

DCO: June 22, 2022

Source: FDA Reviewer – generated analyses based on Applicant submitted data

Treatment with T-DXd appears to result in durable responses in patients with HER2-mutant NSCLC; however, there is limited follow-up available for patients treated with T-DXd at 5.4 mg/kg. Additional follow-up information for DOR will be obtained in the post-marketing setting through an accelerated approval post-marketing requirement.

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Dose/Dose Response

The Applicant's Position:

No additional analyses have been conducted.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Durability of Response

The Applicant's Presentation of Data:

The median DoR based on ICR was 9.3 months (95% CI: 5.7, 14.7) in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study U204 (**Applicant - Table 12**). The estimated proportion of subjects maintaining response based on ICR was estimated to be 60.7% (95% CI: 44.9, 73.2) at 6 months and 45.4% (95% CI: 29.2, 60.2) at 12 months.

The Applicant's Position:

The median DoR demonstrated the persistent clinical benefit of T-DXd 6.4 mg/kg in the HER2-mutant NSCLC population studied.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study results for Study U204. See the preceding section for DoR results for Study U206.

Persistence of Effect

The Applicant's Presentation of Data:

Not applicable.

The Applicant's Position:

Most subjects continued on to further systemic anti-cancer therapy after study drug discontinuation. Persistence of effect was not quantified.

The FDA's Assessment:

FDA agrees with the Applicant's position. Persistence of effect was not quantified for Study U206.

8.1.4 Study Results – Study J101

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Patient Disposition

The Applicant's Presentation of Data:

A total of 11 NSCLC subjects with HER2 mutation were enrolled in Study J101 and were included in the FAS. The median duration of follow-up in subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study J101 was 16.3 months (range: 8.4 to 26.6). One (9.1%) subject was ongoing on treatment with T-DXd 6.4 mg/kg and 10 (90.9%) subjects had discontinued study drug, with PD (72.7%) being the most common reason for discontinuation.

The Applicant's Position:

The most common reason for study drug discontinuation was disease progression as expected for the population studied.

The FDA's Assessment:

FDA acknowledges the Applicant's position. However, FDA did not independently verify the efficacy results of Study J101.

Table of Demographic Characteristics

The Applicant's Presentation of Data:

Key demographic characteristics of subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study J101 are summarized in **Applicant - Table 7**.

The Applicant's Position:

Demographic characteristics were generally consistent with the broader population of patients with HER2-mutant advanced NSCLC seen in clinical practice.

The FDA's Assessment:

FDA acknowledges the Applicant's position. However, FDA did not independently verify the efficacy results of Study J101.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Presentation of Data:

Key baseline characteristics of subjects with HER2 mutation treated with T-DXd 6.4 mg/kg in Study J101 are summarized in **Applicant - Table 7**.

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The Applicant's Position:

Baseline characteristics were generally consistent with the broader population of patients with HER2-mutant advanced NSCLC seen in clinical practice.

The FDA's Assessment:

FDA acknowledges the Applicant's position. However, FDA did not independently verify the efficacy results of Study J101.

Efficacy Results

The Applicant's Presentation of Data:

In Study J101, at DCO:

The confirmed ORR by ICR was 72.7% (95% CI: 39.0, 94.0) in the 11 NSCLC subjects from Part 2d of Study J101 (**Applicant - Table 11**).

The median DoR for confirmed responses by ICR was 9.9 months (95% CI: 6.9, NE).

The DCR by ICR was 90.9% (95% CI: 58.7, 99.8).

The median PFS based on ICR was 11.3 months (95% CI: 8.1, NE).

The median OS was not reached at the time of the DCO. The estimated 6- and 12-month OS rates were 100.0% and 90.9%, respectively.

The Applicant's Position:

Data from subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study J101 supports the strong and clinically meaningful improvement in ORR observed in subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg in Study U204. The observed DoR, DCR, PFS, and OS further support the clinically meaningful antitumor activity of T-DXd in this patient population.

The FDA's Assessment:

FDA acknowledges the Applicant's position. However, FDA did not independently verify the efficacy results of Study J101.

8.1.5 Integrated Review of Effectiveness

The FDA's Assessment:

The efficacy of T-DXd was demonstrated by results from Study U206 and supported by results from Study U204. The Applicant's description of the results from Study J101 also appears to support the primary results from Study U206. In a total of 52 patients with HER2-mutant NSCLC treated with T-DXd

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5.4 mg/kg in the prespecified early cohort as of the June 22, 2022 DCO, the confirmed objective response rate per ICR was 57.7% (95% CI: 43.2, 71.3) where 1 patient had complete response (CR) and 29 patients had partial responses (PR). The median duration of response for the confirmed responders per ICR was 8.7 months (95% CI: 7.1, NE). Among those 30 responders, 18 (60%) patients had an ongoing response without an event.

8.1.6 Assessment of Efficacy Across Trials

Primary Endpoint

The Applicant's Presentation of Data:

The clinical efficacy results from HER2-mutant NSCLC subjects in Study U204 (n = 91), supplemented by HER2-mutant NSCLC subjects from Study J101 (n = 11) treated with T-DXd 6.4 mg/kg, were the primary source for the evaluations of efficacy and benefit/risk of T-DXd for this application. The DCO for the pooled analysis was 03 May 2021 for Study U204 and 01 Aug 2019 for Study J101. The pooling of efficacy data from both studies was supported by the similarities in study design and HER2-mutant NSCLC populations.

The primary population for the pooled efficacy analysis was the FAS defined as all subjects who signed an informed consent and were enrolled in Cohort 2 of Study U024 and Part 2d (HER2-mutant NSCLC) of Study J101. The primary efficacy analysis of the pooled population was based on confirmed responses as determined by ICR based on RECIST v1.1. The primary efficacy analysis in Study U204 was to be conducted after a minimum follow-up of 6 months after the onset of response in all responders in Cohort 2 per the study statistical analysis plan.

Objective Response Rate

Consistent and clinically meaningful confirmed ORRs by ICR were observed in subjects with HER2-mutant NSCLC across the 2 studies (Applicant - Table 11 and [Applicant - Figure 9](#)). The ORR by ICR was 56.9% (95% CI: 46.7, 66.6) in the pooled population. The proportion of subjects with the best overall response of CR was 1.0% for CR, 55.9% for PR, 35.3% for stable disease, and 3.9% for PD.

Applicant - Table 11: *Confirmed ORR by ICR in HER2-Mutant Population (FAS)*

Parameter	Study U204 HER2-Mutant Cohort T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-Mutant Population T-DXd 6.4 mg/kg (N = 11)	Overall HER2-Mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)
Best overall response (confirmed), n (%)			
CR	1 (1.1)	0	1 (1.0)
PR	49 (53.8)	8 (72.7)	57 (55.9)

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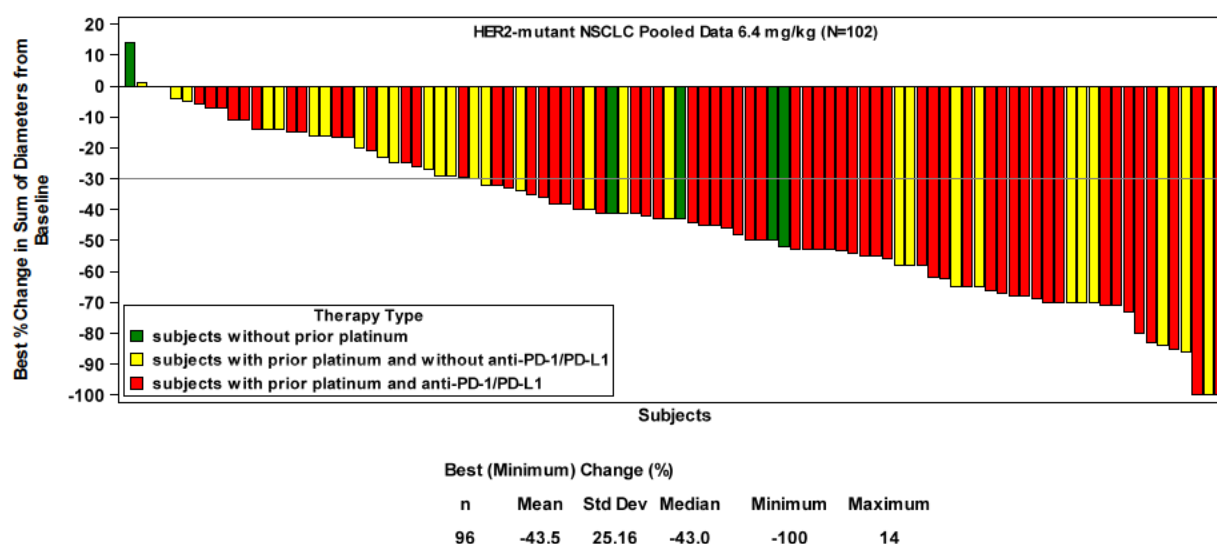
Parameter	Study U204 HER2-Mutant Cohort T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-Mutant Population T-DXd 6.4 mg/kg (N = 11)	Overall HER2-Mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)
SD	34 (37.4)	2 (18.2)	36 (35.3)
PD	3 (3.3)	1 (9.1)	4 (3.9)
NE	4 (4.4)	0	4 (3.9)
Confirmed ORR			
n (%)	50 (54.9)	8 (72.7)	58 (56.9)
95% CI ^a	(44.2, 65.4)	(39.0, 94.0)	(46.7, 66.6)

Pooled data includes 11 subjects from Study J101 and 91 subjects from Study U204. Percentages are based on the number of subjects in the FAS. Tumor assessments were based on RECIST v1.1.

^a The 2-sided 95% CIs are based on the exact (Clopper-Pearson) method for binomial distribution.

DCO date: 03 May 2021 for Study U204 and 01 Aug 2019 for Study J101. Program: t-resp-brsp.sas. Source: ADRS

Applicant - Figure 9: Waterfall Plot of Best (Minimum) Percentage Change in SoD from Baseline in Target Lesions Based on ICR in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (FAS)



For each subject, the best (minimum) percentage change from baseline in the SoD for all target lesions is represented by a vertical bar. There were 2 subjects with best % change of 0.

DCO date: 03 May 2021 for Study U204 and 01 Aug 2019 for Study J101. Program: f-waterfall.sas. Source: ADRS

The Applicant's Position:

The subject population treated in the 2 studies was clearly defined, homogenous, and consistent with

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the target population. The entry criteria in both studies ensured subjects treated with T-DXd would likely benefit from treatment based on its mechanism of action. Demographics and baseline characteristics were similar across the 2 studies. The pooled population was generally representative of the broad population of patients with HER2-mutant NSCLC seen in clinical practice. The pooled population included generally similar proportions of subjects across geographic regions. ORR results demonstrated strong and clinically meaningful antitumor activity.

Secondary and Other Endpoints

Duration of Response

At the DCO, Study J101 provided the longest median duration of study follow-up (16.3 months [range: 8.4 to 26.6]). The median duration of study follow-up was 13.1 months (range: 0.7 to 29.1) in Study U204 and 13.3 months (range: 0.7 to 29.1) for the pooled population.

A clinically meaningful durability of response was consistently observed in subjects with HER2-mutant NSCLC in the pooled population and across the 2 studies: the median DoR by ICR was 9.7 months (95% CI: 6.9, 14.1) in the pooled population (Applicant - Table 12). Based on a Kaplan-Meier analysis, the proportion of subjects in the pooled population maintaining response based on ICR was estimated to be 66.2% (95% CI: 51.7, 77.2) at 6 months and 40.8% (95% CI: 26.0, 55.0) at 12 months.

Applicant - Table 12: DoR by ICR in HER2-mutant Population (FAS)

Parameter	Study U204 HER2-mutant Cohort T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-mutant Population T-DXd 6.4 mg/kg (N = 11)	Overall HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)
Subjects with confirmed CR/PR, n	50	8	58
Subjects with subsequent PD, n (%) ^a	19 (38.0)	5 (62.5)	24 (41.4)
Subjects who subsequently died, n (%) ^a	8 (16.0)	0	8 (13.8)
Subjects censored, n (%) ^a	23 (46.0)	3 (37.5)	26 (44.8)
Median DoR ^b	9.26	9.92	9.69
95% CI ^c	(5.68, 14.65)	(6.93, NE)	(6.93, 14.06)
Subjects with DoR >6 months ^b	24 (48.0)	7 (87.5)	31 (53.4)
Subjects with DoR >12 months ^b	13 (26.0)	1 (12.5)	14 (24.1)
Estimated proportion of subjects with ongoing response at 6 months ^c	60.7	100.0	66.2
95% CI ^c	(44.9, 73.2)	(100.0, 100.0)	(51.7, 77.2)
Estimated proportion of subjects with ongoing response at 12 months ^c	45.4	17.9	40.8

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Parameter	Study U204 HER2-mutant Cohort T-DXd 6.4 mg/kg (N = 91)	Study J101 HER2-mutant Population T-DXd 6.4 mg/kg (N = 11)	Overall HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)
95% CI ^c	(29.2, 60.2)	(0.8, 53.8)	(26.0, 55.0)

Best overall response (CR/PR) with confirmation was assessed by ICR using RECIST v1.1.

Pooled data includes 11 subjects from Study J101 and 91 subjects from Study U204.

For the rows of number of subjects with DoR >6 or >12 months, subjects who had CR or PR response initially and then progressed/dead were counted; subjects who maintained CR/PR response without progression (censoring) with DoR >6 or >12 months were counted; subjects who maintained CR/PR response without progression (censoring) with DoR ≤6 or ≤12 months were not counted.

^a Percentage is calculated using number of subjects with CR/PR as the denominator.

^b Median and estimated proportion of responders maintaining response at 6 and 12 months for DoR are based on Kaplan-Meier estimate.

^c 95% CIs for median and estimated proportion of responders maintaining response at 6 and 12 months for DoR are computed using the Brookmeyer-Crowley method.

DCO date: 03 May 2021 for Study U204 and 01 Aug 2019 for Study J101. Program: t-resp-dor.sas. Source: ADTTE

The Applicant's Position:

Secondary endpoints provide further compelling evidence of efficacy of T-DXd 6.4 mg/kg in the HER2-mutant NSCLC population. Median DoR demonstrated persistent clinical benefit.

The FDA's Assessment:

FDA acknowledges the Applicant's position that the efficacy results are consistent across Study U204 and Study J101. FDA did not independently verify the efficacy results of Study J101 or the pooled efficacy analysis of Study U204 and J101. FDA relies upon the analysis of the 5.4 mg/kg arm of Study U206 as the primary evidence of efficacy, with the other Applicant-presented analyses as supportive only.

Subpopulations

The Applicant's Presentation of Data

In the prespecified subgroups analysis, treatment effect (ORR and DoR based on ICR) was generally consistent across subgroups (age, sex, smoking status, race, country, HER2 mutation status, prior systemic therapy, and number of lines of prior systemic therapy for advanced/metastatic disease) for the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool. Numerical differences were observed between the estimated overall confirmed ORR and DoR based on ICR and the ORR and DoR in some subgroups. However, the corresponding 95% CIs in all subgroups demonstrated overlapping CIs with the corresponding estimated confirmed ORR and DoR in the overall population.

The Applicant's Position:

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There were no clinically meaningful differences in efficacy across subpopulations.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Additionally, there was no meaningful difference in treatment effect (ORR) across subgroups in Study U206.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.7 Integrated Assessment of Effectiveness

The Applicant's Presentation of Data:

The median duration of study follow-up in the HER2-mutant NSCLC T-DXd 6.4 mg/kg pooled population was 13.3 months (range: 0.7 to 29.1) as of the DCO of 03 May 2021.

In the HER2-mutant NSCLC pooled population, T-DXd 6.4 mg/kg demonstrated substantial and durable antitumor activity in subjects with unresectable or metastatic HER2-mutant NSCLC, with a confirmed ORR by ICR in the FAS of 56.9% (95% CI: 46.7, 66.6), a median DoR of 9.7 months (95% CI: 6.9, 14.1), and a median PFS by ICR of 8.3 months (95% CI: 6.9, 11.9). The median OS was 17.8 months (95% CI: 14.0, 22.1). Efficacy was consistent across predefined subgroups.

Clinically meaningful efficacy (ORR, DoR, PFS, OS) was observed in subjects in the HER2-mutant NSCLC pooled population treated with T-DXd 6.4 mg/kg.

The observed ORR and durability of response with T-DXd at 6.4 mg/kg in subjects with unresectable or metastatic HER2-mutant NSCLC who have received at least 1 prior therapy substantially exceed the efficacy observed with currently available therapies in the metastatic setting ([Applicant - Table](#)). The lower bound of the 95% CI for ORR with T-DXd was higher than the upper bound of the 95% CI for ORR with the ramucirumab plus docetaxel regimen and other approved therapies. Note that efficacy results from published literature shown in [Applicant - Table](#) for currently available therapies are for NSCLC patients regardless of HER2 status, except for T-DXd clinical trials. Data from published literature suggests a possible trend for poorer clinical outcomes on treatment with currently available therapies for patients with NSCLC with activating HER2 mutation compared with HER2 wild-type NSCLC.

The Applicant's Position:

T-DXd is the first therapy targeting HER2-mutant NSCLC that demonstrates consistent and clinically

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meaningful efficacy with strong and durable responses in this patient population, addressing a high unmet medical need. Overall, clinically meaningful efficacy was observed in the T-DXd 6.4 mg/kg HER2-mutant pooled population. Efficacy was consistent across subgroups. The ORR and durability of response with T-DXd in subjects with unresectable or metastatic HER2-mutant NSCLC who have received at least 1 prior therapy substantially exceed those of currently available therapies in the metastatic setting, addressing a high unmet medical need. The lower bound of the 95% CI for ORR with T-DXd (46.7%) is higher than the upper bound of the 95% CI for ORR with the ramucirumab plus docetaxel regimen (26.4%) and other approved therapies.

The FDA's Assessment:

FDA agrees with the Applicant's conclusion that the efficacy results demonstrated clinically meaningful and durable antitumor response of T-DXd in patients with unresectable or metastatic *HER2* mutant NSCLC who have received at least one prior therapy. The evidence of efficacy was consistent across prespecified subgroups and supported by Study U204 and Applicant-presented analyses from Study J101. FDA considers time-to-event endpoints such as PFS and OS to be uninterpretable in single-arm settings and are considered descriptive only.

8.2 REVIEW OF SAFETY

The Applicant's Presentation of Data:

A comprehensive review of the safety data of T-DXd in NSCLC at the 6.4 mg/kg and 5.4 mg/kg doses along with a review of the safety profile of T-DXd across all tumor types and at dose levels 5.4 mg/kg and above was conducted (Applicant - Table 13).

Applicant - Table 13: Safety Pools

Safety Pools	Studies Included in Pooled Analyses	Number of Treated Subjects
HER2-Mutant NSCLC T-DXd 6.4 mg/kg Pool	J101 (n = 11), U204 (n = 91)	102
NSCLC T-DXd 6.4 mg/kg Pool	J101 (n = 18), U204 (n = 140)	158
All Tumor Types T-DXd 6.4 mg/kg Pool	J101 (n = 183), U201 (n = 48), J202 (n = 169), U204 (n = 140)	540
NSCLC T-DXd 5.4 mg/kg Pool ^a	U204 (n = 41; Cohort 1a HER2-overexpressing)	41
All Tumor Types T-DXd 5.4 mg/kg Pool	J101 (n = 91), U201 (n = 184), U204 (n = 41)	316
All Tumor Types T-DXd ≥5.4 mg/kg Pool	J101 (n = 280), U201 (n = 169), J202 (n = 253), U204 (n = 181)	883

Data are included as of DCO of 01 Aug 2019 for Study J101, 08 Jun 2020 for Study U201, 03 Jun 2020 for Study J202, and 03 May 2021 for Study U204.

^a No subjects with HER2-mutant NSCLC were treated with T-DXd 5.4 mg/kg.

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The Applicant's Position:

Available safety data allowed for a comprehensive and adequate assessment of the safety profile of T-DXd, including detection and characterization of common AEs, guidance on toxicity management, and an evaluation of the overall benefit-risk in adult patients in the target population. Pooling of safety data from HER2-mutant and HER2-overexpressing subjects with NSCLC treated with T-DXd 6.4 mg/kg is supported by a similarity of the established safety profiles.

The FDA's Assessment:

FDA disagrees with the Applicant's original position. The review of safety data not only included safety data from Study U204 and J101, but also included safety data from Study U206. The primary safety population included the cohort of patients in Study U206 treated at the 5.4 mg/kg dose level (data cutoff March 24, 2022).

8.2.1 Safety Review Approach

The Applicant's Presentation of Data:

AEs (classified using Medical Dictionary for Regulatory Activities [MedDRA] version 23.0) were considered TEAEs from the first dose of the study drug until 47 days (for all studies except Study J101 [28 days]) after the last dose of study drug. Severity of AEs and laboratory parameters was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. To increase the accuracy of the estimate of incidence of TEAEs, selected preferred terms (PTs) for analogous terms in MedDRA were combined into grouped terms as shown in **Applicant - Table 14**.

Applicant - Table 14: MedDRA PTs Combined into Grouped Terms

Grouped Term	MedDRA PTs
Abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
Anemia	anaemia, haemoglobin decreased, haematocrit decreased, red blood cell count decreased
Fatigue	fatigue, asthenia, malaise
Headache	headache, migraine, sinus headache
Leukopenia	leukopenia, white blood cell count decreased
Lymphopenia	lymphopenia, lymphocyte count decreased
Neutropenia	neutropenia, neutrophil count decreased
Rash	rash, rash pustular, rash maculo-papular
Stomatitis	stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering

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Grouped Term	MedDRA PTs
Thrombocytopenia	thrombocytopenia, platelet count decreased
URTI	upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, ^a pharyngitis, ^a sinusitis, ^a rhinitis ^a

^a For clinical groupings of PTs specific to ADRs, the following new PTs have been identified: nasopharyngitis, pharyngitis, sinusitis, and rhinitis for the existing grouped PT of URTI. The ADR summary table uses this new grouping for summarizing URTI as a medical concept.

In addition to the grouped terms, the following individual PTs were selected for additional characterization for the T-DXd program: nausea, decreased appetite, diarrhoea, vomiting, constipation, febrile neutropenia.

The Applicant has identified ILD/pneumonitis and left ventricular (LV) dysfunction as adverse events of special interest (AESIs) for the T-DXd program. For LV dysfunction, relevant PTs were reviewed by the Applicant. All potential ILD/pneumonitis events were reviewed by an independent ILD AC.

The safety analyses include notable differences (≥10 percentage points) in the incidence of TEAEs between the pools unless specified otherwise.

The Applicant's Position:

The safety review approach was considered comprehensive to identify and characterize the key differences between the pooled groups.

The FDA's Assessment:

FDA generally agrees with the Applicant's approach; however, FDA has applied this approach to the primary safety population in Study U206.

8.2.2 Review of the Safety Database

Overall Exposure

The Applicant's Presentation of Data:

The median (range) treatment duration in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool was 7.3 months (0.7 to 26.4). Median treatment duration varied across different pools, ranging from 4.8 to 8.3 months.

The Applicant's Position:

The exposure to T-DXd was considered adequate to allow for a comprehensive assessment of safety in subjects who were representative of the target population. The median relative dose intensity indicated

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that T-DXd regimen was manageable and tolerable for most subjects.

The FDA's Assessment:

FDA agrees with the Applicant's position. In Study U206, the median treatment duration in the T-DXd 5.4 mg/kg arm was 3.7 months (range: 0.7 to 11.8 months). The median treatment duration in the T-DXd 6.4 mg/kg arm was 3.3 months (range: 0.7 to 12.6 months). Although treatment duration in the primary safety population was relatively short, the safety information in patients with NSCLC is supported by Study U204 and Study J101 with longer duration of follow-up noted above.

Relevant characteristics of the safety population:

The Applicant's Presentation of Data:

Key demographics and baseline characteristics for this pool are presented in **Applicant - Table 15** and **Applicant - Table 16**, respectively.

Applicant - Table 15: Key Demographic Characteristics (Safety Analysis Set)

Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Sex, n (%)							
Male	31 (34.1)	34 (33.3)	66 (41.8)	238 (44.1)	22 (53.7)	35 (11.1)	274 (31.0)
Female	60 (65.9)	68 (66.7)	92 (58.2)	302 (55.9)	19 (46.3)	281 (88.9)	609 (69.0)
Age (years)							
Mean (SD)	60.3 (11.94)	59.9 (12.62)	60.6 (11.71)	60.0 (11.52)	60.3 (10.22)	57.3 (11.71)	59.0 (11.65)
Median	60.0	60.0	61.5	62.0	62.0	58.0	60.0
Min, max	29, 88	23, 88	23, 88	23, 88	31, 76	28, 96	23, 96
Age category, n (%) ^a							
<65 years	55 (60.4)	62 (60.8)	94 (59.5)	326 (60.4)	27 (65.9)	221 (69.9)	565 (64.0)
≥65 years	36 (39.6)	40 (39.2)	64 (40.5)	214 (39.6)	14 (34.1)	95 (30.1)	318 (36.0)
<75 years	80 (87.9)	90 (88.2)	144 (91.1)	498 (92.2)	39 (95.1)	299 (94.6)	824 (93.3)
≥75 years	11 (12.1)	12 (11.8)	14 (8.9)	42 (7.8)	2 (4.9)	17 (5.4)	59 (6.7)
Race, n (%)							
White	40 (44.0)	47 (46.1)	79 (50.0)	138 (25.6)	31 (75.6)	167 (52.8)	316 (35.8)

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Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Asian	31 (34.1)	35 (34.3)	53 (33.5)	366 (67.8)	4 (9.8)	122 (38.6)	503 (57.0)
Other	20 (22.0)	20 (19.6)	26 (16.5)	35 (6.5)	6 (14.6)	23 (7.3)	59 (6.7)
Missing	0	0	0	1 (0.2)	0	4 (1.3)	5 (0.6)
Country, n (%)							
Japan	23 (25.3)	26 (25.5)	43 (27.2)	309 (57.2)	3 (7.3)	74 (23.4)	397 (45.0)
Non-Japan	68 (74.7)	76 (74.5)	115 (72.8)	231 (42.8)	38 (92.7)	242 (76.6)	486 (55.0)

^a Subject's age is the age at the date of signing informed consent. Program: t-demo.sas. Source data: ADSL

Enhertu[®] (fam-trastuzumab deruxtecan-nxki)**Applicant - Table 16: Key Baseline Characteristics (Safety Analysis Set)**

Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Baseline ECOG PS, n (%)							
0	23 (25.3)	26 (25.5)	41 (25.9)	257 (47.6)	5 (12.2)	170 (53.8)	446 (50.5)
1	68 (74.7)	76 (74.5)	117 (74.1)	283 (52.4)	36 (87.8)	145 (45.9)	436 (49.4)
2	0	0	0	0	0	1 (0.3)	1 (0.1)
Baseline smoking status, n (%)							
Current	2 (2.2)	2 (2.0)	7 (4.4)	8 (1.5)	2 (4.9)	13 (4.1)	21 (2.4)
Previous	37 (40.7)	37 (36.3)	65 (41.1)	74 (13.7)	30 (73.2)	62 (19.6)	139 (15.7)
Never	52 (57.1)	52 (51.0)	68 (43.0)	106 (19.6)	9 (22.0)	150 (47.5)	274 (31.0)
Missing/unknown	0	11 (10.8)	18 (11.4)	352 (65.2)	0	91 (28.8)	449 (50.8)
Baseline renal function, n (%)							
Normal renal function	31 (34.1)	36 (35.3)	58 (36.7)	209 (38.7)	13 (31.7)	140 (44.3)	359 (40.7)
Mild renal impairment	37 (40.7)	41 (40.2)	65 (41.1)	212 (39.3)	17 (41.5)	126 (39.9)	353 (40.0)
Moderate renal impairment	22 (24.2)	24 (23.5)	33 (20.9)	116 (21.5)	11 (26.8)	49 (15.5)	167 (18.9)
Severe renal impairment	1 (1.1)	1 (1.0)	2 (1.3)	2 (0.4)	0	1 (0.3)	3 (0.3)
Missing/unknown	0	0	0	1 (0.2)	0	0	1 (0.1)
Baseline hepatic function, n (%)							
Normal hepatic function	82 (90.1)	90 (88.2)	141 (89.2)	379 (70.2)	38 (92.7)	193 (61.1)	590 (66.8)
Mild hepatic impairment	9 (9.9)	12 (11.8)	17 (10.8)	159 (29.4)	3 (7.3)	120 (38.0)	288 (32.6)
Moderate hepatic impairment	0	0	0	1 (0.2)	0	1 (0.3)	2 (0.2)
Severe hepatic impairment	0	0	0	0	0	0	0

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Parameter	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Missing/unknown	0	0	0	1 (0.2)	0	2 (0.6)	3 (0.3)
Prior pneumonectomy, n (%)							
Yes	20 (22.0)	20 (19.6)	33 (20.9)	NA	7 (17.1)	NA	NA
No	71 (78.0)	82 (80.4)	125 (79.1)	NA	34 (82.9)	NA	NA
Prior pleural effusion, n (%)							
Yes	7 (7.7)	10 (9.8)	16 (10.1)	NA	2 (4.9)	NA	NA
No	84 (92.3)	92 (90.2)	142 (89.9)	NA	39 (95.1)	NA	NA
Number of lines of prior systemic therapy for advanced/metastatic disease, n (%)							
≤2	61 (67.0)	63 (61.8)	90 (57.0)	228 (42.2)	21 (51.2)	70 (22.2)	306 (34.7)
>2	30 (33.0)	39 (38.2)	68 (43.0)	312 (57.8)	20 (48.8)	246 (77.8)	577 (65.3)
Prior anti-PD-1 or PD-L1 therapy, n (%)							
Yes	60 (65.9)	68 (66.7)	110 (69.6)	NA	33 (80.5)	NA	NA
No	31 (34.1)	34 (33.3)	48 (30.4)	NA	8 (19.5)	NA	NA

Program: t-demo.sas. Source data: ADSL

The Applicant's Position

The safety database includes a molecularly defined and homogenous population that is sufficiently diverse to adequately represent the target population.

The FDA's Assessment:

FDA agrees with the Applicant's position. The key demographics of the primary safety population in Study U206 (Table 17, T-DXd 5.4 mg/kg arm) are similar to those in Study U204 with the exception that Study U206 enrolled a larger percentage of patients from Asian countries. Given the high percentage of patients in Study U204 in North American sites, these data in total appear to be representative of a diverse U.S. population.

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Table 17: Demographic Characteristics of Safety Population (Study U206)

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Gender		
Female	65 (64)	34 (68)
Male	36 (36)	16 (32)
Age		
Mean (SD)	59 (12)	59 (12)
Median (Min - Max)	59 (30 - 84)	60 (27 - 85)
Age Group		
>=40,	57 (56)	33 (66)
>=65,	32 (32)	10 (20)
>=75	8 (8)	5 (10)
>=18,	4 (4.0)	2 (4.0)
ECOG		
1	71 (70)	31 (62)
0	30 (30)	19 (38)
Race		
Asian	64 (63)	31 (62)
White	23 (23)	5 (10)
Other	14 (14)	12 (24)
Black or African American	0 (0)	2 (4.0)
Ethnicity		
Not Hispanic or Latino	88 (87)	41 (82)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Unknown	12 (12)	8 (16)
Hispanic or Latino	1 (1.0)	1 (2.0)
Country		
Japan	37 (37)	15 (30)
South Korea	18 (18)	10 (20)
France	14 (14)	12 (24)
Italy	9 (9)	1 (2.0)
Taiwan	7 (7)	5 (10)
Netherlands	6 (6)	2 (4.0)
Spain	4 (4.0)	2 (4.0)
USA	3 (3.0)	1 (2.0)
Australia	2 (2.0)	1 (2.0)
Canada	1 (1.0)	1 (2.0)
History of brain metastasis		
No	59 (58)	26 (52)
Yes	42 (42)	24 (48)
CNS Metastasis		
No	68 (67)	28 (56)
Yes	33 (33)	22 (44)
Liver Metastasis		
No	77 (76)	35 (70)
Yes	24 (24)	15 (30)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Number of Lines of Prior Systemic Therapy for Advanced/Metastatic Disease		
<=2	68 (67)	31 (62)
>2	33 (33)	19 (38)
Prior Cancer Radiation Therapy		
Yes	57 (56)	25 (50)
No	44 (44)	25 (50)
Prior Cancer Surgery		
No	75 (74)	37 (74)
Yes	26 (26)	13 (26)
Prior Platinum-based Therapy		
Yes	101 (100)	50 (100)
Prior Anti PD-1 Therapy		
Yes	58 (57)	29 (58)
No	43 (43)	21 (42)
Prior Anti PD-L1 Therapy		
No	78 (77)	38 (76)
Yes	23 (23)	12 (24)
Prior Platinum/Anti PD-(L)1 Not in Combo		
No	75 (74)	39 (78)
Yes	26 (26)	11 (22)
Prior Platinum/Anti PD-(L)1 In Combo		
No	53 (52)	22 (44)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Yes	48 (48)	28 (56)
Number of Prior Regimens		
2	33 (33)	20 (40)
1	31 (31)	10 (20)
5	10 (10)	1 (2.0)
3	10 (10)	8 (16)
4	8 (8)	9 (18)
8	3 (3.0)	0 (0)
6	2 (2.0)	1 (2.0)
7	2 (2.0)	1 (2.0)
11	1 (1.0)	0 (0)
12	1 (1.0)	0 (0)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, SEX, AAGE, AGEGR1, ECOGBL, RACE, ETHNIC, COUNTRY, BRAINMET, CNSMET, LIVERMET, NPRESYSN, NPRESYS, PCANR, PCANS, PCAT1, PCAT3, PCAT4, PCAT5, PCAT6, REGIMN

Adequacy of the safety database:

The Applicant's Presentation of Data:

The safety database for this submission included 102 NSCLC subjects with HER2 mutation who were assigned to T-DXd 6.4 mg/kg dose in Studies U204 and J101 (see **Applicant - Table 16** for the number of subjects in other pools). Median treatment duration was 7.3 months (range: 0.7 to 26.4) for this pool.

The Applicant's Position:

The available safety database allows for an adequate assessment of the overall safety profile of T-DXd in the targeted population.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the adequacy of the available safety database;

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however, this FDA's assessment is based on a primary safety population including 101 patients in the T-DXd 5.4 mg/kg arm of Study U206. These data are supported by safety data from patients treated with T-DXd 6.4 mg/kg in Study U206, Study U204, and Study J101.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Presentation of Data:

The Applicant's quality control and quality assurance activities, data management and statistical analysis of the study data were implemented per the Applicant's GCP standard operation procedures. Monitors designated by the Applicant to ensure compliance of the investigators and other site staff members involved in this study were granted direct access to the source documents maintained at individual study sites and verified that case report form data were accurately reported and consistent with the source data. As applicable, contract research organizations and central laboratories implemented data quality control activities based on their relevant in-house standard operation procedures. All potential ILD cases were submitted to an independent ILD AC.

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections by the Applicant; data in the case report forms and AE databases were consistent.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The data submitted was organized and adequate to perform a complete review of the safety of T-DXd.

Categorization of Adverse Event

The Applicant's Presentation of Data:

The safety profile observed with T-DXd was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of AEs to study treatment.

- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs associated with study drug discontinuation, dose reduction, study drug interruption, and AESI).

- Frequency and type of AEs in key intrinsic and extrinsic factors (e.g., age, ECOG PS, renal and hepatic function at baseline, geographic region, and country).

- Changes in laboratory variables, with particular attention to abnormalities of CTCAE Grade 3 or 4.

The Applicant's Position:

The categorization of AEs was considered appropriate for evaluating the safety data in the targeted population treated with T-DXd at the target dose.

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The FDA's Assessment:

The FDA agrees with the Applicant's categorization of adverse events (AEs) for the primary and supportive safety populations. Adverse events were coded using MedDRA version 24.1 and were graded according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0). The safety assessment focused on the frequency and severity of all treatment-emergent AEs (TEAEs). A TEAE was defined as an AE that occurred during the study period, that was absent before the first dose of study drug or has worsened in severity or seriousness after initiating the study drug until 47 days after the last dose of the study drug. Serious adverse events (SAEs) with an onset or worsening 48 days or more after the last dose of study drug, if considered related to study treatment, were also TEAEs. Additional analyses included assessment of TEAEs leading to death, SAEs, and TEAEs leading to dose reduction, interruption, or permanent discontinuation of T-DXd. The FDA review was completed using MedDRA preferred terms (PTs) and CTCAE grade.

Routine Clinical Tests

The Applicant's Presentation of Data:

The tables of study procedures and scheduled assessments in the protocols for the individual studies specified the time points at which laboratory evaluations were conducted. Per protocol, abnormal laboratory values considered clinically significant by the investigator were to be reported as AEs.

The Applicant's Position:

The clinical monitoring of subject safety (methods and time points) described in the protocols was considered to be appropriate and adequate for the population, disease, and targeted indication being investigated.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4 Safety Results

Deaths

The Applicant's Presentation of Data:

As of the DCO of each individual study, deaths due to any cause (including deaths that occurred during follow-up) were reported in 50.0% of subjects in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (**Applicant - Table 18**). On-treatment deaths (as defined in the footnote to **Applicant - Table 18**) were reported in 12.7% of subjects. The most common cause of on treatment death was disease progression and AE.

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Applicant - Table 18: Deaths by Primary Cause and On-treatment Deaths (Safety Analysis Set)

Primary Cause of Death	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Any death	47 (51.6)	51 (50.0)	88 (55.7)	289 (53.5)	11 (26.8)	106 (33.5)	408 (46.2)
Primary cause of any death							
Adverse event	6 (6.6)	6 (5.9)	11 (7.0)	25 (4.6)	1 (2.4)	10 (3.2)	37 (4.2)
Disease progression	33 (36.3)	37 (36.3)	67 (42.4)	233 (43.1)	7 (17.1)	72 (22.8)	315 (35.7)
Unknown	3 (3.3)	3 (2.9)	4 (2.5)	19 (3.5)	1 (2.4)	14 (4.4)	34 (3.9)
Other	5 (5.5)	5 (4.9)	6 (3.8)	12 (2.2)	2 (4.9)	10 (3.2)	22 (2.5)
On-treatment death ^a	13 (14.3)	13 (12.7)	23 (14.6)	41 (7.6)	5 (12.2)	15 (4.7)	58 (6.6)
Primary cause of on-treatment death							
Adverse event	6 (6.6)	6 (5.9)	10 (6.3)	18 (3.3)	0	5 (1.6)	24 (2.7)
Disease progression	6 (6.6)	6 (5.9)	12 (7.6)	22 (4.1)	3 (7.3)	7 (2.2)	30 (3.4)
Unknown	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	1 (2.4)	1 (0.3)	2 (0.2)
Other	0	0	0	0	1 (2.4)	2 (0.6)	2 (0.2)

^a On-treatment deaths = death between 1st dose and 28 days (for Study J101)/47 days (for all other studies) after the last dose .

Program: t-death.sas. Source data: ADSL

The most common PT associated with an outcome of death (reported in ≥2 subjects) in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool was disease progression ([Applicant - Table](#)).

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Applicant - Table 19: TEAEs Associated with an Outcome of Death by PT (Safety Analysis Set)

MedDRA PT	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N=91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N=102)	NSCLC Pool T-DXd 6.4 mg/kg (N=158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N=540)	NSCLC Pool T-DXd 5.4 mg/kg (N=41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N=316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N=883)
Subjects with any TEAE associated with an outcome of death	13 (14.3)	13 (12.7)	24 (15.2)	45 (8.3)	5 (12.2)	18 (5.7)	66 (7.5)
Disease progression	7 (7.7)	7 (6.9)	13 (8.2)	20 (3.7)	3 (7.3)	5 (1.6)	26 (2.9)
Pneumonitis	1 (1.1)	1 (1.0)	2 (1.3)	5 (0.9)	0	2 (0.6)	9 (1.0)
Respiratory failure	0	0	2 (1.3)	2 (0.4)	0	3 (0.9)	5 (0.6)
Acute pulmonary oedema	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Bronchospasm	0	0	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Dyspnoea	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Hydrocephalus	0	0	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Intestinal perforation	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Pneumocystis jirovecii pneumonia	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Seizure	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	0	1 (0.1)
Acute hepatic failure	0	0	0	0	0	1 (0.3)	1 (0.1)
Acute kidney injury	0	0	0	0	0	1 (0.3)	1 (0.1)
Acute respiratory failure	0	0	0	0	0	1 (0.3)	1 (0.1)
Asthenia	0	0	0	1 (0.2)	0	0	1 (0.1)
Disseminated intravascular coagulation	0	0	0	2 (0.4)	0	0	2 (0.2)
Febrile neutropenia	0	0	0	1 (0.2)	0	0	1 (0.1)
General physical health deterioration	0	0	0	0	0	1 (0.3)	1 (0.1)

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MedDRA PT	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N=91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N=102)	NSCLC Pool T-DXd 6.4 mg/kg (N=158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N=540)	NSCLC Pool T-DXd 5.4 mg/kg (N=41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N=316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N=883)
Hepatic function abnormal	0	0	0	1 (0.2)	0	0	1 (0.1)
Interstitial lung disease	0	0	0	1 (0.2)	0	0	1 (0.1)
Large intestine perforation	0	0	0	1 (0.2)	0	0	1 (0.1)
Lymphangitis	0	0	0	0	0	1 (0.3)	1 (0.1)
Mechanical ileus	0	0	0	1 (0.2)	0	0	1 (0.1)
Neoplasm malignant	0	0	0	0	1 (2.4)	1 (0.3)	1 (0.1)
Neoplasm progression	0	0	0	2 (0.4)	0	0	2 (0.2)
Pneumonia	0	0	0	1 (0.2)	0	1 (0.3)	2 (0.2)
Pneumonia aspiration	0	0	0	1 (0.2)	0	0	1 (0.1)
Sepsis	0	0	0	0	1 (2.4)	1 (0.3)	1 (0.1)
Shock haemorrhagic	0	0	0	0	0	1 (0.3)	1 (0.1)
Upper gastrointestinal haemorrhage	0	0	0	1 (0.2)	0	0	1 (0.1)

Program: t-teae-bypt.sas. Source data: ADAE

The Applicant's Position:

A review of deaths across the studies did not identify any pattern and most deaths were associated with disease progression, few on-treatment deaths (mostly PD) were observed.

The FDA's Assessment:

FDA agrees with the Applicant's position. Most deaths in the primary safety population in Study U206 were associated with disease progression (**Table 20**). There was one death associated with a TEAE in each arm of Study U206. FDA considers both deaths to be related to ILD/pneumonitis (Section 8.2.5.1). This is a known serious risk associated with T-DXd and is addressed in product labeling with a boxed warning. As patients with *HER2*-mutant NSCLC are frequently managed by thoracic oncologists, who

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have experience managing other drug-related pulmonary toxicities, patients in this population will typically have access to appropriate medical care to identify and mitigate the risks associated with ILD/pneumonitis.

Table 20: Summary of Deaths (Study U206)

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Total Deaths	13 (13)	6 (12)
Disease Progression	12 (12)	5 (10)
Adverse Event	1 (1.0)	1 (2.0)
Within 30 days after last dose	3 (3.0)	3 (6)
Disease Progression	2 (2.0)	2 (4.0)
Adverse Event	1 (1.0)	1 (2.0)
Beyond 30 days after last dose	10 (10)	3 (6)
Disease Progression	10 (10)	3 (6)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, DTHCAUS, DTHDT, DTHFL, TRTEDT

Serious Adverse Events

The Applicant's Presentation of Data:

Treatment-emergent SAEs were reported in 39.2% of the subjects in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (**Applicant - Table 21**). The most common SAEs in this population (reported in ≥2% of subjects) were adjudicated drug related ILD, disease progression, seizure, vomiting, central nervous system necrosis, pleural effusion, and pneumonia (**Applicant - Table 21**).

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Applicant - Table 21: Treatment-emergent SAE by PT or Grouped Term Based on a Cut-off of ≥1% Subjects in the NSCLC T-DXd 6.4 mg/kg Pool (Safety Analysis Set)

MedDRA PT or Grouped Term	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
ILD	10 (11.0)	11 (10.8)	16 (10.1)	34 (6.3)	1 (2.4)	15 (4.7)	52 (5.9)
Disease progression	7 (7.7)	7 (6.9)	13 (8.2)	20 (3.7)	3 (7.3)	5 (1.6)	26 (2.9)
Pneumonia	2 (2.2)	2 (2.0)	6 (3.8)	17 (3.1)	1 (2.4)	9 (2.8)	27 (3.1)
Dyspnoea	1 (1.1)	1 (1.0)	5 (3.2)	5 (0.9)	1 (2.4)	2 (0.6)	8 (0.9)
Seizure	3 (3.3)	3 (2.9)	4 (2.5)	4 (0.7)	0	1 (0.3)	5 (0.6)
Vomiting	3 (3.3)	3 (2.9)	4 (2.5)	8 (1.5)	1 (2.4)	5 (1.6)	13 (1.5)
Nausea	1 (1.1)	1 (1.0)	3 (1.9)	7 (1.3)	0	3 (0.9)	10 (1.1)
CNS necrosis	2 (2.2)	2 (2.0)	2 (1.3)	2 (0.4)	0	0	2 (0.2)
Diarrhoea	1 (1.1)	1 (1.0)	2 (1.3)	4 (0.7)	1 (2.4)	2 (0.6)	6 (0.7)
Mental status changes	1 (1.1)	1 (1.0)	2 (1.3)	2 (0.4)	0	0	2 (0.2)
Pleural effusion	2 (2.2)	2 (2.0)	2 (1.3)	2 (0.4)	1 (2.4)	4 (1.3)	7 (0.8)
Respiratory failure	0	0	2 (1.3)	3 (0.6)	0	5 (1.6)	8 (0.9)

Program: t-teae-bypt.sas; t-sild.pt.sas; t-teae-slec-gp.sas. Source data: ADAE

The Applicant's Position:

The most common SAEs in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool were generally manageable by dose modification and routine clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's position. For the primary safety population in Study U206 serious adverse events (SAEs) occurred in 30% of patients receiving T-DXd 5.4 mg/kg (**Table 22**). SAEs in >1% of patients who received T-DXd 5.4 mg/kg were interstitial lung disease (ILD)/pneumonitis (4%) dyspnea (2%), nausea (2%), pleural effusion (2%), and increased troponin I (2%). The risk of serious ILD/pneumonitis is consistent with other currently approved indications and is adequately addressed by product labeling.

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Table 22: Treatment-emergent SAEs (Study U206)

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Patients with serious AEs	30 (30)	16 (32)
Respiratory, Thoracic And Mediastinal Disorders		
Pneumonitis (GT)	4 (4.0)	1 (2.0)
Dyspnea (GT)	2 (2.0)	0 (0)
Pleural Effusion	2 (2.0)	0 (0)
Pulmonary Embolism	1 (1.0)	0 (0)
Respiratory Failure	1 (1.0)	0 (0)
Gastrointestinal Disorders		
Nausea	2 (2.0)	0 (0)
Diarrhea (GT)	1 (1.0)	3 (6)
Duodenal Ulcer	1 (1.0)	0 (0)
Ileus	1 (1.0)	0 (0)
Intestinal Perforation	1 (1.0)	0 (0)
Large Intestinal Obstruction	1 (1.0)	0 (0)
Vomiting (GT)	1 (1.0)	0 (0)
Odynophagia	0 (0)	1 (2.0)
Investigations		
Troponin I Increased	2 (2.0)	0 (0)
Neutrophil Count Decreased	1 (1.0)	2 (4.0)
Platelet Count Decreased	1 (1.0)	2 (4.0)
Troponin Increased	1 (1.0)	0 (0)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
General Physical Condition Abnormal	0 (0)	1 (2.0)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)		
Malignant Neoplasm Progression	2 (2.0)	0 (0)
Cancer Pain	1 (1.0)	0 (0)
Lung Neoplasm Malignant	1 (1.0)	0 (0)
General Disorders And Administration Site Conditions		
Fatigue (GT)	1 (1.0)	2 (4.0)
General Physical Health Deterioration	1 (1.0)	0 (0)
Pyrexia (GT)	1 (1.0)	0 (0)
Malaise	0 (0)	1 (2.0)
Infections And Infestations		
Covid-19	1 (1.0)	0 (0)
Pneumonia (GT)	1 (1.0)	1 (2.0)
Urinary Tract Infection (GT)	1 (1.0)	1 (2.0)
Post Procedural Infection	0 (0)	1 (2.0)
Blood And Lymphatic System Disorders		
Thrombocytopenia	1 (1.0)	0 (0)
Anemia	0 (0)	2 (4.0)
Cardiac Disorders		
Acute Myocardial Infarction	1 (1.0)	0 (0)
Endocrine Disorders		
Hypothyroidism (GT)	1 (1.0)	0 (0)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Eye Disorders		
Optic Nerve Disorder	1 (1.0)	0 (0)
Musculoskeletal And Connective Tissue Disorders		
Musculoskeletal Pain (GT)	1 (1.0)	0 (0)
Renal And Urinary Disorders		
Ureteric Obstruction	1 (1.0)	0 (0)
Acute Kidney Injury (GT)	0 (0)	1 (2.0)
Nervous System Disorders		
Hydrocephalus	0 (0)	1 (2.0)
Neurological Symptom	0 (0)	1 (2.0)
Metabolism And Nutrition Disorders		
Dehydration	0 (0)	1 (2.0)
Psychiatric Disorders		
Disorientation	0 (0)	1 (2.0)

Group Pneumonitis (GT) includes PT terms INTERSTITIAL LUNG DISEASE, PNEUMONITIS,

Group Fatigue (GT) includes PT terms FATIGUE,

Group Dyspnea (GT) includes PT terms DYSPNOEA,

Group Diarrhea (GT) includes PT terms DIARRHOEA, COLITIS, ENTEROCOLITIS,

Group Urinary Tract Infection (GT) includes PT terms URINARY TRACT INFECTION,

Group Pneumonia (GT) includes PT terms PNEUMONIA,

Group Vomiting (GT) includes PT terms VOMITING,

Group Hypothyroidism (GT) includes PT terms HYPOTHYROIDISM,

Group Pyrexia (GT) includes PT terms PYREXIA,

Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN,

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Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY,

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADAE (Adverse Event Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Presentation of Data:

In the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, 34.3% of subjects had TEAEs associated with study drug discontinuation (**Applicant - Table 23**). The most common TEAEs (reported in ≥2% of subjects) associated with study drug discontinuation were adjudicated drug-related ILD, disease progression, and pneumonitis.

Applicant - Table 23: TEAEs Associated with Study Drug Discontinuation by PT or Grouped Term Based on a Cut-off of ≥1% Subjects in the NSCLC T-DXd 6.4 mg/kg Pool (Safety Analysis Set)

MedDRA PT or Grouped Term	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Subjects with any TEAEs associated with study drug discontinuation	34 (37.4)	35 (34.3)	52 (32.9)	135 (25.0)	6 (14.6)	54 (17.1)	202 (22.9)
ILD	16 (17.6)	17 (16.7)	28 (17.7)	72 (13.3)	1 (2.4)	28 (8.9)	108 (12.2)
Disease progression	4 (4.4)	4 (3.9)	6 (3.8)	7 (1.3)	2 (4.9)	2 (0.6)	9 (1.0)
Pneumonia	0	0	2 (1.3)	5 (0.9)	0	2 (0.6)	9 (1.0)
Pneumonitis ^a	2 (2.2)	2 (2.0)	2 (1.3)	8 (1.5)	1 (2.4)	4 (1.3)	13 (1.5)
Respiratory failure ^a	0	0	2 (1.3)	3 (0.6)	0	0	3 (0.3)

^a In addition to the events of pneumonitis and respiratory failure that are included in the grouped term of adjudicated drug-related ILD, some subjects with pneumonitis or respiratory failure are included separately under the PTs of pneumonitis or respiratory failure, because the PTs were either adjudicated as not being ILD, were adjudicated as being ILD but not related to T-DXd, or were pending adjudication at the time of DCO.

Program: t-teae-bypt.sas; t-ild-pt.sas; t-teae-slec-gpc.sas. Source data: ADAE

The Applicant's Position:

In the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, TEAEs associated with study drug discontinuation

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were largely due to events of adjudicated drug-related ILD.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. For the primary safety population in Study U206 T-DXd 5.4 mg/kg was permanently discontinued due to a treatment-emergent adverse event (TEAE) in 8% of patients (**Table 24**). TEAEs which resulted in permanent discontinuation of T-DXd 5.4 mg/kg were ILD/pneumonitis (6%), diarrhea (1%), hypokalemia (1%), hypomagnesemia (1%), myocarditis (1%), and vomiting (1%). The risk of ILD/pneumonitis is consistent with other currently approved indications and is adequately addressed by product labeling.

Table 24: TEAEs Associated with Study Drug Discontinuation (Study U206)

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Study treatment - drug withdrawn - due to AEs	8 (8)	8 (16)
Pneumonitis (GT)	5 (5.0)	6 (12)
Diarrhoea (GT)	1 (1.0)	0 (0)
Hypokalemia	1 (1.0)	0 (0)
Hypomagnesemia	1 (1.0)	0 (0)
Myocarditis	1 (1.0)	0 (0)
Pulmonary Toxicity	1 (1.0)	0 (0)
Vomiting (GT)	1 (1.0)	0 (0)
Acute Kidney Injury (GT)	0 (0)	1 (2.0)
Pneumonia (GT)	0 (0)	1 (2.0)

Group Vomiting (GT) includes PT terms VOMITING, RETCHING,

Group Diarrhea (GT) includes PT terms DIARRHEA, COLITIS, ENTEROCOLITIS,

Group Pneumonitis (GT) includes PT terms INTERSTITIAL LUNG DISEASE, PNEUMONITIS,

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA CYTOMEGALOVIRAL,

Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY, RENAL FAILURE, RENAL TUBULAR DISORDER,

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADAE (Adverse Event Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

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Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Presentation of Data:

In the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, TEAEs associated with dose reduction were reported in 34.3% of subjects. The most common (reported in ≥2% of subjects) TEAEs associated with dose reduction were fatigue (grouped term) (13.7%), nausea (9.8%), neutropenia (grouped term) (2.9%), anemia (grouped term), febrile neutropenia, and weight decreased (2.0% each).

In the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, TEAEs associated with study drug interruption were reported in 48.0% of subjects. The most common (reported in ≥2% of subjects) TEAEs associated with study drug interruption were neutropenia (grouped term) (13.7%), adjudicated drug-related ILD (7.8%), pneumonia (5.9%), anemia (grouped term) (4.9%), fatigue (grouped term) (3.9%), leukopenia (grouped term) (2.9%), blood bilirubin increased, seizure, thrombocytopenia (grouped term), and upper respiratory tract infection (grouped term) (2.0%, each).

The Applicant's Position:

Observed TEAEs associated with dose reduction or study drug interruption were generally manageable and as expected in this patient population.

The FDA's Assessment:

FDA agrees with the Applicant's position. Dose reductions and interruptions in the primary safety population (5.4 mg/kg arm of Study U206) appeared to be manageable given the context of this serious, life-threatening disease.

For the primary safety population in Study U206, dose reductions of T-DXd 5.4 mg/kg due to a TEAE occurred in 11% of patients (**Table 25**). TEAEs (≥2%) which required dose reduction were decreased appetite and thrombocytopenia.

For the primary safety population in Study U206, dose interruptions of T-DXd 5.4 mg/kg due to a TEAE occurred in 23% of patients (**Table 26**). TEAEs which required dosage interruption (≥2%) included neutropenia, ILD/pneumonitis, pneumonia, anemia, and COVID-19 infection.

Table 25: TEAEs Associated with Study Drug Dose Reduction (Study U206)

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Study treatment - dose reduced - due to AEs	11 (11)	13 (26)
Decreased Appetite	2 (2.0)	1 (2.0)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Platelet Count Decreased	2 (2.0)	2 (4.0)
Alanine Aminotransferase Increased	1 (1.0)	0 (0)
Blood Bilirubin Increased	1 (1.0)	0 (0)
Covid-19	1 (1.0)	0 (0)
Diarrhea (GT)	1 (1.0)	0 (0)
Fatigue (GT)	1 (1.0)	1 (2.0)
Nausea	1 (1.0)	3 (6)
Neutrophil Count Decreased	1 (1.0)	5 (10)
Urinary Tract Infection (GT)	1 (1.0)	0 (0)
Weight Decreased	1 (1.0)	0 (0)
Anemia	0 (0)	1 (2.0)
Febrile Neutropenia	0 (0)	1 (2.0)
Malaise	0 (0)	1 (2.0)
Vomiting (GT)	0 (0)	1 (2.0)
White Blood Cell Count Decreased	0 (0)	1 (2.0)

Group Vomiting (GT) includes PT terms VOMITING, RETCHING,

Group Diarrhea (GT) includes PT terms DIARRHOEA, COLITIS, ENTEROCOLITIS,

Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,

Group Urinary Tract Infection (GT) includes PT terms URINARY TRACT INFECTION, CYSTITIS,

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADAE (Adverse Event Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Enhertu[®] (fam-trastuzumab deruxtecan-nxki)**Table 26: TEAEs Associated with Study Drug Interruption (Study U206)**

	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Study treatment - drug interrupted - due to AEs	23 (23)	18 (36)
Neutrophil Count Decreased	6 (6)	6 (12)
Anemia	2 (2.0)	3 (6)
Covid-19	2 (2.0)	1 (2.0)
Pneumonia (GT)	2 (2.0)	0 (0)
Pneumonitis (GT)	2 (2.0)	1 (2.0)
Alanine Aminotransferase Increased	1 (1.0)	0 (0)
Aspartate Aminotransferase Increased	1 (1.0)	0 (0)
Dyspnea (GT)	1 (1.0)	0 (0)
Ejection Fraction Decreased	1 (1.0)	0 (0)
Fatigue (GT)	1 (1.0)	3 (6)
General Physical Health Deterioration	1 (1.0)	0 (0)
Neutropenia	1 (1.0)	5 (10)
Pharyngitis	1 (1.0)	0 (0)
Platelet Count Decreased	1 (1.0)	2 (4.0)
Pyrexia (GT)	1 (1.0)	1 (2.0)
Respiratory Failure	1 (1.0)	0 (0)
Troponin I Increased	1 (1.0)	0 (0)
Troponin Increased	1 (1.0)	0 (0)
Diarrhea (GT)	0 (0)	2 (4.0)
White Blood Cell Count Decreased	0 (0)	2 (4.0)

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	T-DXD 5.4 MG/KG N = 101 N (%)	T-DXD 6.4 MG/KG N = 50 N (%)
Blood Bilirubin Increased	0 (0)	1 (2.0)
Hydrocephalus	0 (0)	1 (2.0)
Odynophagia	0 (0)	1 (2.0)
Urinary Tract Infection (GT)	0 (0)	1 (2.0)

Group Diarrhoea (GT) includes PT terms DIARRHEA, COLITIS, ENTEROCOLITIS,

Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,

Group Pyrexia (GT) includes PT terms PYREXIA,

Group Pneumonitis (GT) includes PT terms INTERSTITIAL LUNG DISEASE, PNEUMONITIS,

Group Dyspnea (GT) includes PT terms DYSPNEA, DYSPNEA EXERTIONAL,

Group Urinary Tract Infection (GT) includes PT terms URINARY TRACT INFECTION, CYSTITIS,

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA CYTOMEGALOVIRAL,

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADAE (Adverse Event Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Significant Adverse Events

The Applicant's Presentation of Data:

Among TEAEs/grouped terms selected for additional characterization for the T-DXd program, the most common selected TEAEs/grouped terms in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool were GI or hematologic in nature. The most common selected TEAEs/grouped terms ≥Grade 3 (reported in ≥10% of subjects) were neutropenia (grouped term) (17.6%) and anemia (grouped term) (11.8%).

There were 3 events considered to be an infusion related reaction in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool.

The Applicant's Position:

The most common selected TEAEs/grouped terms were GI or hematologic in nature, which is expected for this class of drugs and were manageable by dose modification and routine clinical practice. The available safety database was considered adequate to categorize these events for the target population.

The FDA's Assessment:

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FDA agrees with the Applicant's position. Adverse events of special interest are addressed in Section 8.2.5.1 (interstitial lung disease) and Section 8.2.5.2 (left ventricular dysfunction).

Treatment-emergent Adverse Events and Adverse Reactions

The Applicant's Presentation of Data:

All subjects in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool had at least 1 TEAE, with 69.6% having TEAEs of ≥Grade 3 (**Applicant - Table 27**).

Applicant - Table 27: Overview of TEAEs (Safety Analysis Set)

Parameter	Number (%) of Subjects						
	Study U204 HER2- mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Treatment duration (months)							
Mean (SD)	8.67 (6.376)	8.90 (6.182)	7.83 (6.095)	8.29 (7.251)	4.60 (2.944)	10.51 (7.952)	9.10 (7.517)
Median	6.90	7.31	6.16	5.82	4.83	8.26	6.90
Min, max	0.7, 26.4	0.7, 26.4	0.7, 26.4	0.7, 41.0	0.7, 9.6	0.7, 37.9	0.7, 41.0
Subjects with any TEAE, n (%)	91 (100.0)	102 (100.0)	158 (100.0)	540 (100.0)	41 (100.0)	314 (99.4)	881 (99.8)
TEAEs with CTCAE ≥Grade 3	63 (69.2)	71 (69.6)	114 (72.2)	405 (75.0)	20 (48.8)	177 (56.0)	602 (68.2)
SAE	39 (42.9)	40 (39.2)	68 (43.0)	205 (38.0)	14 (34.1)	83 (26.3)	298 (33.7)
TEAEs associated with study drug discontinuation	34 (37.4)	35 (34.3)	52 (32.9)	132 (24.4)	6 (14.6)	51 (16.1)	196 (22.2)
TEAEs associated with dose reduction	32 (35.2)	35 (34.3)	53 (33.5)	180 (33.3)	7 (17.1)	64 (20.3)	258 (29.2)

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Parameter	Number (%) of Subjects						
	Study U204 HER2- mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
TEAEs associated with study drug interruption	44 (48.4)	49 (48.0)	75 (47.5)	272 (50.4)	10 (24.4)	126 (39.9)	413 (46.8)
TEAEs associated with an outcome of death	13 (14.3)	13 (12.7)	24 (15.2)	45 (8.3)	5 (12.2)	18 (5.7)	66 (7.5)

Program: t-ex.sas; t-teae-sum.sas. Source data: ADEXSUM and ADAE

The most common TEAEs were primarily GI or hematologic in nature (**Applicant - Table 28** **Applicant - Table 28**).

Applicant - Table 28: TEAEs Reported in ≥20% of Subjects in NSCLC T-DXd 6.4 mg/kg Pool, by PT/Grouped Term (Safety Analysis Set)

MedDRA PT or Grouped Term	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Most common (≥20% of subjects in NSCLC T-DXd 6.4 mg/kg Pool) TEAEs of all grades							
Nausea	69 (75.8)	77 (75.5)	112 (70.9)	388 (71.9)	30 (73.2)	246 (77.8)	651 (73.7)
Fatigue	55 (60.4)	60 (58.8)	94 (59.5)	319 (59.1)	27 (65.9)	200 (63.3)	538 (60.9)
Vomiting	42 (46.2)	48 (47.1)	67 (42.4)	209 (38.7)	12 (29.3)	142 (44.9)	359 (40.7)
Decreased appetite	32 (35.2)	38 (37.3)	66 (41.8)	307 (56.9)	19 (46.3)	118 (37.3)	433 (49.0)
Alopecia	42 (46.2)	47 (46.1)	61 (38.6)	201 (37.2)	5 (12.2)	123 (38.9)	335 (37.9)
Constipation	34 (37.4)	40 (39.2)	56 (35.4)	176 (32.6)	10 (24.4)	106 (33.5)	294 (33.3)
Diarrhoea	37 (40.7)	40 (39.2)	56 (35.4)	192 (35.6)	14 (34.1)	101 (32.0)	301 (34.1)

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MedDRA PT or Grouped Term	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Neutropenia	32 (35.2)	37 (36.3)	53 (33.5)	241 (44.6)	4 (9.8)	88 (27.8)	346 (39.2)
Anaemia	33 (36.3)	38 (37.3)	52 (32.9)	242 (44.8)	10 (24.4)	101 (32.0)	355 (40.2)
ILD	24 (26.4)	26 (25.5)	38 (24.1)	97 (18.0)	2 (4.9)	42 (13.3)	148 (16.8)
Weight decreased	21 (23.1)	24 (23.5)	37 (23.4)	96 (17.8)	6 (14.6)	32 (10.1)	135 (15.3)
Dyspnoea	18 (19.8)	20 (19.6)	33 (20.9)	51 (9.4)	9 (22.0)	50 (15.8)	104 (11.8)
Leukopenia	21 (23.1)	25 (24.5)	33 (20.9)	167 (30.9)	2 (4.9)	60 (19.0)	241 (27.3)
Most common (≥5% of subjects in NSCLC T-DXd 6.4 mg/kg Pool) ≥Grade 3 TEAEs							
Neutropenia	17 (18.7)	18 (17.6)	31 (19.6)	163 (30.2)	0	51 (16.1)	222 (25.1)
Anaemia	10 (11.0)	12 (11.8)	16 (10.1)	132 (24.4)	2 (4.9)	29 (9.2)	166 (18.8)
Disease progression	7 (7.7)	7 (6.9)	13 (8.2)	20 (3.7)	3 (7.3)	5 (1.6)	26 (2.9)
Fatigue	6 (6.6)	6 (5.9)	13 (8.2)	48 (8.9)	3 (7.3)	21 (6.6)	75 (8.5)
Lymphopenia	10 (11.0)	10 (9.8)	12 (7.6)	43 (8.0)	1 (2.4)	15 (4.7)	61 (6.9)
Nausea	8 (8.8)	9 (8.8)	12 (7.6)	30 (5.6)	2 (4.9)	19 (6.0)	51 (5.8)
ILD	6 (6.6)	7 (6.9)	11 (7.0)	21 (3.9)	1 (2.4)	10 (3.2)	34 (3.9)
Pneumonia	3 (3.3)	3 (2.9)	9 (5.7)	17 (3.1)	2 (4.9)	8 (2.5)	26 (2.9)
Leukopenia	4 (4.4)	5 (4.9)	8 (5.1)	76 (14.1)	0	17 (5.4)	97 (11.0)

Program: t-teae-bypt.sas; t-ild-pt.sas; t-teae-slec-gpc.sas. Source data: ADAE

Adverse Drug Reactions

No new adverse drug reactions (ADRs) were identified for this population in comparison to the identified T-DXd ADRs. The most common (incidence >5%) ≥Grade 3 ADRs in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool were neutropenia (grouped term), anemia (grouped term), lymphopenia (grouped term), nausea, and fatigue (grouped term) (**Applicant - Table 29**).

Among the 102 subjects in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, 19.6% had ADRs associated with study drug discontinuation, 29.4% had ADRs associated with dose reduction, and 31.4% had ADRs associated with study drug interruption.

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Applicant - Table 29: Common ADRs (≥10% of Subjects with Events of Any Grade or ≥2% of Subjects with Events of Grade 3 or 4) by CTCAE Grade in the NSCLC T-DXd ≥5.4 mg/kg Pool and HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool by MedDRA SOC and PT or Grouped Term (Safety Analysis Set)

MedDRA SOC and PT or Grouped Term	Number (%) of Subjects			
	NSCLC T-DXd ≥5.4 mg/kg Pool (N = 199)		HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (N = 102)	
	CTCAE Grade		CTCAE Grade	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Nausea	142 (71.4)	14 (7.0)	77 (75.5)	9 (8.8)
Vomiting	79 (39.7)	8 (4.0)	48 (47.1)	5 (4.9)
Constipation	66 (33.2)	0	40 (39.2)	0
Diarrhoea	70 (35.2)	7 (3.5)	40 (39.2)	3 (2.9)
Abdominal pain	25 (12.6)	1 (0.5)	13 (12.7)	0
Blood and lymphatic system disorders				
Anaemia	62 (31.2)	18 (9.0)	38 (37.3)	12 (11.8)
Neutropenia	57 (28.6)	31 (15.6)	37 (36.3)	18 (17.6)
Leukopenia	35 (17.6)	8 (4.0)	25 (24.5)	5 (4.9)
Lymphopenia	24 (12.1)	13 (6.5)	18 (17.6)	10 (9.8)
Thrombocytopenia	31 (15.6)	7 (3.5)	18 (17.6)	5 (4.9)
Febrile neutropenia	4 (2.0)	4 (2.0)	2 (2.0)	2 (2.0)
General disorders and administration site conditions				
Fatigue	121 (60.8)	16 (8.0)	60 (58.8)	6 (5.9)
Skin and subcutaneous tissue disorders				
Alopecia	66 (33.2)	0	47 (46.1)	0
Rash	12 (6.0)	0	12 (11.8)	0
Metabolism and nutrition disorders				
Decreased appetite	85 (42.7)	3 (1.5)	38 (37.3)	1 (1.0)
Hypokalaemia	27 (13.6)	5 (2.5)	15 (14.7)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				

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MedDRA SOC and PT or Grouped Term	Number (%) of Subjects			
	NSCLC T-DXd ≥5.4 mg/kg Pool (N = 199)		HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (N = 102)	
	CTCAE Grade		CTCAE Grade	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
ILD ^a	40 (20.1)	5 (2.5)	26 (25.5)	5 (4.9)
Dyspnoea	42 (21.1)	6 (3.0)	20 (19.6)	0
Investigations				
AST increased	28 (14.1)	2 (1.0)	19 (18.6)	0
ALT increased	23 (11.6)	2 (1.0)	15 (14.7)	0
Infections and infestations				
URTI	26 (13.1)	0	16 (15.7)	0
Nervous system disorders				
Headache	22 (11.1)	1 (0.5)	16 (15.7)	1 (1.0)

^a ILD in the NSCLC ≥5.4 mg/kg pool includes events that were adjudicated as ILD: pneumonitis*, interstitial lung disease*, respiratory failure, and lung opacity* (*: observed also in HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool).

Program: t-cadr-event-adruass.sas. Source data: ADADR

The Applicant's Position:

The observed TEAEs were as expected in this population, with the most commonly reported TEAEs (including ≥Grade 3 TEAEs) being GI or hematologic in nature. TEAEs were generally manageable by dose modifications and routine clinical practice. After a comprehensive review, the list of T-DXd ADRs was also as expected for the anti-HER2 class of drugs.

The FDA's Assessment:

FDA agrees that TEAEs observed in the *HER2*-mutant NSCLC population were consistent with commonly reported TEAEs for this drug product across indications. Data from the primary safety population (T-DXd 5.4 mg/kg arm in Study U206) are presented below (**Table 30**).

The most common (≥20%) TEAEs in the primary safety population were nausea, fatigue, constipation, decreased appetite, vomiting, and alopecia. These risks are consistent with the known safety profile of T-DXd. No non-laboratory Grade 3-4 TEAEs occurred in greater than 5% of the primary safety population. Non-laboratory Grade 3-4 TEAEs that occurred in more than one patient included fatigue (4%), nausea (3%), vomiting (2%) and pneumonitis (2%).

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Table 30: TEAEs Occurring in ≥ 10% by Grouped Terms (U206)

	T-DXD 5.4 MG/KG N = 101		T-DXD 6.4 MG/KG N = 50	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	97 (96)	37 (37)	50 (100)	28 (56)
Gastrointestinal Disorders				
Nausea	62 (61)	3 (3.0)	40 (80)	3 (6)
Constipation	31 (31)	1 (1.0)	14 (28)	0 (0.0)
Vomiting (GT)	26 (26)	2 (2.0)	22 (44)	1 (2.0)
Diarrhea (GT)	19 (19)	1 (1.0)	15 (30)	3 (6)
Stomatitis (GT)	12 (12)	0 (0.0)	2 (4.0)	0 (0.0)
Abdominal Pain (GT)	9 (9)	0 (0.0)	6 (12)	0 (0.0)
Investigations				
Neutrophil Count Decreased	28 (28)	10 (10)	19 (38)	13 (26)
White Blood Cell Count Decreased	23 (23)	3 (3.0)	15 (30)	7 (14)
Platelet Count Decreased	18 (18)	3 (3.0)	9 (18)	5 (10)
Aspartate Aminotransferase Increased	14 (14)	1 (1.0)	4 (8)	0 (0.0)
Alanine Aminotransferase Increased	13 (13)	2 (2.0)	6 (12)	0 (0.0)
Weight Decreased	3 (3.0)	1 (1.0)	5 (10)	0 (0.0)
Metabolism And Nutrition Disorders				
Decreased Appetite	30 (30)	1 (1.0)	21 (42)	2 (4.0)
General Disorders And Administration Site Conditions				
Fatigue (GT)	32 (32)	4 (4.0)	15 (30)	3 (6)
Pyrexia (GT)	9 (9)	0 (0.0)	6 (12)	0 (0.0)

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	T-DXD 5.4 MG/KG N = 101		T-DXD 6.4 MG/KG N = 50	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Blood And Lymphatic System Disorders				
Anemia	34 (34)	10 (10)	20 (40)	7 (14)
Neutropenia	6 (6)	2 (2.0)	7 (14)	5 (10)
Respiratory, Thoracic And Mediastinal Disorders				
Pneumonitis (GT)	7 (7)	2 (2.0)	8 (16)	0 (0.0)
Cough (GT)	6 (6)	0 (0.0)	5 (10)	0 (0.0)
Dyspnea (GT)	6 (6)	1 (1.0)	6 (12)	0 (0.0)
Skin And Subcutaneous Tissue Disorders				
Alopecia	21 (21)	0 (0.0)	16 (32)	1 (2.0)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)	15 (15)	1 (1.0)	4 (8)	0 (0.0)

Group Fatigue (GT) includes PT terms ASTHENIA, FATIGUE, MALAISE

Group Diarrhea (GT) includes PT terms DIARRHEA, COLITIS, ENTEROCOLITIS,

Group Vomiting (GT) includes PT terms VOMITING, RETCHING,

Group Pneumonitis (GT) includes PT terms INTERSTITIAL LUNG DISEASE, PNEUMONITIS,

Group Dyspnea (GT) includes PT terms DYSPNOEA, DYSPNOEA EXERTIONAL,

Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN, MUSCULOSKELETAL STIFFNESS, ARTHRALGIA, MYALGIA, NECK PAIN, MUSCULOSKELETAL PAIN, MUSCULOSKELETAL CHEST PAIN, PAIN IN EXTREMITY,

Group Pyrexia (GT) includes PT terms PYREXIA,

Group Cough (GT) includes PT terms COUGH, PRODUCTIVE COUGH,

Group Stomatitis (GT) includes PT terms MUCOSAL INFLAMMATION, STOMATITIS,

Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN UPPER, ABDOMINAL PAIN, ABDOMINAL DISCOMFORT,

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADAE (Adverse Event Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

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Laboratory Findings**The Applicant's Presentation of Data:****Applicant - Table 31: Laboratory Abnormality ADRs (Safety Analysis Set)**

Laboratory Abnormality	Number (%) of Subjects			
	NSCLC T-DXd ≥5.4 mg/kg Pool (N = 199)		HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool (N = 102)	
	CTCAE Grade		CTCAE Grade	
	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4
Hematology				
Anaemia (hemoglobin decreased)	122/195 (62.6)	11/195 (5.6)	71/101 (70.3)	8/101 (7.9)
White blood cell decreased	122/195 (62.6)	12/195 (6.2)	67/101 (66.3)	7/101 (6.9)
Lymphocyte count decreased	103/195 (52.8)	41/195 (21.0)	59/101 (58.4)	24/101 (23.8)
Neutrophil count decreased	98/195 (50.3)	21/195 (10.8)	54/101 (53.5)	9/101 (8.9)
Platelet count decreased	65/194 (33.5)	5/194 (2.6)	38/101 (37.6)	3/101 (3.0)
Chemistry				
AST increased	76/196 (38.8)	0/196	47/102 (46.1)	0/102
ALT increased	67/196 (34.2)	0/196	41/102 (40.2)	0/102
Hypokalemia	37/196 (18.9)	4/196 (2.0)	28/102 (27.5)	1/102 (1.0)

Program: t-abno-adruss.sas. Source data: ADLB

The Applicant's Position:

Laboratory abnormalities were consistent with the observed TEAEs in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool and generally consistent across other doses in this population.

The FDA's Assessment:

FDA agrees with the Applicant's position. Laboratory abnormalities in the primary safety population (T-DXd 5.4 mg/kg arm in Study U206) were consistent with the supportive safety data reported by the Applicant above (**Table 32**). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin count, decreased white blood cell count, decreased platelet count, hypokalemia, and increased alanine aminotransferase. Decreased neutrophil count, decreased hemoglobin count, and decreased lymphocyte count are established risks with T-DXd and are appropriately addressed by product labelling.

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Table 32: Laboratory Abnormalities Occurring in ≥ 10% by Grouped Terms (U206)

	T-DXD 5.4 MG/KG N = 101		T-DXD 6.4 MG/KG N = 50	
	Grades 1-4 n/N evaluatable (%)	Grades 3-4 n/N evaluatable (%)	Grades 1-4 n/N evaluatable (%)	Grades 3-4 n/N evaluatable (%)
LACTATE DEHYDROGENASE (UKAT/L) - Increased	9/99 (9)	0/99 (0.0)	10/49 (20)	0/49 (0.0)
LEUKOCYTES (10 ⁹ /L) - Decreased	59/99 (60)	4/99 (4.0)	34/50 (68)	8/50 (16)
ASPARTATE AMINOTRANSFERASE (UKAT/L) - Increased	35/99 (35)	1/99 (1.0)	20/50 (40)	0/50 (0.0)
HEMOGLOBIN (G/L) - Decreased	57/99 (58)	10/99 (10)	30/50 (60)	7/50 (14)
NEUTROPHILS (10 ⁹ /L) - Decreased	51/99 (52)	12/99 (12)	32/50 (64)	17/50 (34)
LYMPHOCYTES (10 ⁹ /L) - Decreased	42/98 (43)	16/98 (16)	20/48 (42)	5/48 (10)
ALKALINE PHOSPHATASE (UKAT/L) - Increased	22/99 (22)	0/99 (0.0)	12/50 (24)	1/50 (2.0)
ALANINE AMINOTRANSFERASE (UKAT/L) - Increased	34/99 (34)	2/99 (2.0)	17/50 (34)	0/50 (0.0)
PLATELETS (10 ⁹ /L) - Decreased	40/99 (40)	4/99 (4.0)	20/50 (40)	3/50 (6)
ALBUMIN (G/L) - Decreased	39/99 (39)	0/99 (0.0)	16/50 (32)	1/50 (2.0)
SODIUM (MMOL/L) - Decreased	34/99 (34)	3/99 (3.0)	13/50 (26)	0/50 (0.0)
CREATININE (UMOL/L) - Increased	8/99 (8)	1/99 (1.0)	12/50 (24)	1/50 (2.0)
POTASSIUM (MMOL/L) - Increased	13/99 (13)	0/99 (0.0)	6/50 (12.0)	0/50 (0.0)
POTASSIUM (MMOL/L) - Decreased	17/99 (17)	2/99 (2.0)	16/50 (32)	4/50 (8)
BILIRUBIN (UMOL/L) - Increased	3/99 (3.0)	1/99 (1.0)	6/50 (12)	0/50 (0.0)
ACTIVATED PARTIAL THROMBOPLASTIN TIME (SEC) - Increased	1/5 (20)	0/5 (0.0)	0/0 (0.0)	0/0 (0.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-06-16, ADLB (Laboratory Tests Analysis Dataset) - 2022-06-16. Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, TRTEDT, ADT, TRTSDT, ADY, ATOXGRN

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Vital Signs

The Applicant's Presentation of Data:

Vital sign parameters included heart rate, systolic and diastolic blood pressure, temperature, and peripheral oxygen saturation. In general, no clinically meaningful change from baseline were observed in any of the vital sign parameters.

The Applicant's Position:

No clinically relevant changes in vital signs or trends over time were observed.

The FDA's Assessment:

FDA agrees with the Applicant's position. There was no clinically meaningful change from baseline in heart rate, systolic and diastolic blood pressure, temperature, and peripheral oxygen saturation in Study U206.

QT Prolongation

The Applicant's Presentation of Data:

No subject in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool had a new QT interval corrected for heart rate using Fridericia's formula (QTcF) value >500 ms or a new QT interval value of >500 ms.

Of the 7 (6.9%) subjects with TEAEs of electrocardiogram QT prolonged in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, 1 (1.0%) was associated with study drug interruption. There were no study drug discontinuations or dose reductions.

The Applicant's Position:

T-DXd was not associated with QT prolongation.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. There were no TEAEs of electrocardiogram QT prolongation in the T-DXd 5.4 mg/kg arm of Study U206. In this population (n=68 with measurements), the mean change in the QT interval from baseline to the maximum post-baseline value was 5.3 msec (range: -72.3 to 71.3 msec).

Immunogenicity

The Applicant's Presentation of Data:

Immunogenicity was reported as part of pharmacology (Section 6.3.1).

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The Applicant's Position:

See Section 6.3.1.

The FDA's Assessment:

FDA agrees that immunogenicity risks remain low for T-DXd 5.4 mg/kg in the NSCLC setting and are consistent with the immunogenicity profile in other disease settings. There were no TEAEs of hypersensitivity in the T-DXd 5.4 mg/kg arm in Study U206.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Interstitial Lung Disease

The Applicant's Presentation of Data:

As of the DCO, all potential events of ILD/pneumonitis were submitted to the ILD AC. In the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool, 25.5% subjects were determined to have adjudicated drug-related ILD (**Applicant - Table 33**). Adjudicated drug-related ILD events were mostly Grade 1 (3.9%) or Grade 2 (14.7%). Five (4.9%) subjects had Grade 3 events and 2 (2.0%) had Grade 5 events.

Applicant - Table 33: ILD Events by Adjudicated Outcome and Adjudicated Grade (Safety Analysis Set)

CTCAE Grade Reported by AC ^a	Number (%) of Subjects						
	Study U204 HER2-mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2-mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Subjects with any AE adjudicated as drug-related ILD	24 (26.4)	26 (25.5)	38 (24.1)	97 (18.0)	2 (4.9)	42 (13.3)	148 (16.8)
Adjudicated CTCAE grade							
Grade 1	3 (3.3)	4 (3.9)	7 (4.4)	27 (5.0)	0	8 (2.5)	37 (4.2)
Grade 2	15 (16.5)	15 (14.7)	20 (12.7)	49 (9.1)	1 (2.4)	24 (7.6)	77 (8.7)
Grade 3	4 (4.4)	5 (4.9)	5 (3.2)	9 (1.7)	0	2 (0.6)	12 (1.4)
Grade 4	0	0	0	1 (0.2)	0	0	1 (0.1)
Grade 5	2 (2.2)	2 (2.0)	6 (3.8)	11 (2.0)	1 (2.4)	8 (2.5)	21 (2.4)
≥Grade 3	6 (6.6)	7 (6.9)	11 (7.0)	21 (3.9)	1 (2.4)	10 (3.2)	34 (3.9)

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CTCAE Grade Reported by AC ^a	Number (%) of Subjects						
	Study U204 HER2- mutant NSCLC T-DXd 6.4 mg/kg (N = 91)	HER2- mutant NSCLC Pool T-DXd 6.4 mg/kg (N = 102)	NSCLC Pool T-DXd 6.4 mg/kg (N = 158)	All Tumor Types Pool T-DXd 6.4 mg/kg (N = 540)	NSCLC Pool T-DXd 5.4 mg/kg (N = 41)	All Tumor Types Pool T-DXd 5.4 mg/kg (N = 316)	All Tumor Types Pool T-DXd ≥5.4 mg/kg (N = 883)
Serious ILD	10 (11.0)	11 (10.8)	16 (10.1)	34 (6.3)	1 (2.4)	15 (4.7)	52 (5.9)
Action taken							
Dose reduction	1 (1.1)	1 (1.0)	1 (0.6)	1 (0.2)	0	4 (1.3)	5 (0.6)
Study drug interruption	8 (8.8)	8 (7.8)	9 (5.7)	24 (4.4)	0	7 (2.2)	31 (3.5)
Study drug discontinuation	16 (17.6)	17 (16.7)	28 (17.7)	72 (13.3)	1 (2.4)	28 (8.9)	108 (12.2)
Outcome ^b							
Fatal	1 (4.2)	1 (3.8)	3 (7.9)	7 (7.2)	0	6 (14.3)	15 (10.1)
Not recovered/not resolved	7 (29.2)	9 (34.6)	12 (31.6)	43 (44.3)	2 (100.0)	14 (33.3)	60 (40.5)
Recovering/resolving	2 (8.3)	2 (7.7)	2 (5.3)	11 (11.3)	0	1 (2.4)	13 (8.8)
Recovered/resolved with sequelae	1 (4.2)	1 (3.8)	1 (2.6)	1 (1.0)	0	1 (2.4)	4 (2.7)
Recovered/resolved	13 (54.2)	13 (50.0)	18 (47.4)	33 (34.0)	0	18 (42.9)	52 (35.1)
Ongoing	0	0	0	0	0	1 (2.4)	1 (0.7)
Missing/unknown	0	0	2 (5.3)	2 (2.1)	0	1 (2.4)	3 (2.0)
Treatment of adjudicated drug-related ILD ^c							
Steroid(s)	21 (23.1)	22 (21.6)	31 (19.6)	66 (12.2)	2 (4.9)	26 (8.2)	98 (11.1)
Antibiotic(s)	10 (11.0)	11 (10.8)	17 (10.8)	33 (6.1)	1 (2.4)	12 (3.8)	48 (5.4)
Steroid(s) and antibiotic(s)	9 (9.9)	10 (9.8)	16 (10.1)	30 (5.6)	1 (2.4)	10 (3.2)	43 (4.9)
Median (range) time to adjudicated onset of first event (days) ^d	141.0 (14, 462)	160.5 (14, 462)	138.0 (2, 462)	165.0 (2, 680)	118.0 (46, 190)	246.5 (42, 660)	186.0 (2, 680)
Median (range) duration of first event (days) ^{e,f}	43.0 (24.0, 94.0)	43.0 (29.0, 94.0)	41.0 (37.0, 94.0)	134.0 (51.0, 157.0)	NA (NA, NA)	66.0 (29.0, 137.0)	121.0 (51.0, 147.0)

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^a The ILD AC assigned grades to potential ILD/pneumonitis events that were adjudicated as ILD.

^b The outcome of the worst ILD event denominator was based on the adjudicated as drug-related ILD.

^c Treatment of ILD included the antibiotics/steroids used/reported by the investigators for subjects with adjudicated drug-related ILD events.

^d Time to first investigator reported ILD onset (days) = onset date of first investigator reported ILD adjudicated as drug-related – first dose date + 1.

ⁱ Duration of first ILD = investigator reported end date – investigator reported onset date + 1. End date will be censored for ongoing ILDs.

^f Median was based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley.

Program: t-ild-pt.sas; t-sild-pt.sas; t-ild-drug-rel.sas; t-ild-pneu.sas. Source data: ADAE

The Applicant's Position:

ILD/pneumonitis is a known serious risk for T-DXd and has been closely monitored from the beginning of the clinical study program. A well-established safety evaluation process was followed and robust data collection and adjudication by the independent ILD AC ensured a comprehensive assessment of the ILD events, and an adequate management plan for ongoing studies. ILD requires proper monitoring, dose modification, and supportive care instituted in a timely fashion.

In clinical trials of T-DXd across multiple tumor types and doses, the overall safety profile of T-DXd is consistent and there is no notable difference observed for the risk of ILD/pneumonitis. For the prescriber, the management of this AE is the same irrespective of the tumor type or dose. Based on this assessment and to provide a more precise numerical estimate of this AE in the T-DXd-treated patient population, the Applicant has proposed (b) (4) is presented for ILD in the Warnings and Precautions of the USPI.

The FDA's Assessment:

FDA disagrees with the Applicant's position. The incidence of ILD/pneumonitis in Study U204 (26%) was greater than reported for gastric cancer (10%) and metastatic breast cancer (9%). The reason for this increased incidence is unclear, however it may be due to the receipt of prior radiation therapy (58%) and prior anti-PD-(L)1 agents (66%).

In the dose-optimization Study U206 in *HER2*-mutant NSCLC, the incidence of ILD/pneumonitis was 6% in the T-DXd 5.4 mg/kg arm (primary safety population) and 14% in the T-DXd 6.4 mg/kg arm. Only one event was ≥ Grade 3 in each arm, but both events were fatal.

The patient with Grade 5 ILD/pneumonitis in the T-DXd 5.4 mg/kg arm (Patient# (b) (6)) was a 73-year-old woman with NSCLC who had received prior treatment with pembrolizumab. On cycle 2, Study Day 42, the patient developed Grade 3 pneumonitis related to T-DXd per investigator assessment. The

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patient had worsening oxygen saturation and a COVID-19 test was negative. High-resolution CT demonstrated “diffuse ground-glass opacities, with suspicion of pneumonitis”. An echocardiogram showed Grade 1 pulmonary hypertension. Despite intensive care, the patient died two days later. This TEAE was adjudicated by the independent ILD adjudication committee as not ILD, noting “that the baseline scan showed coronary calcification, enlarged heart, and evidence of pulmonary venous hypertension” and documenting the event as “not ILD but cardiac source of CT changes and death.” Based on the available data and the investigator assessment of pneumonitis related to T-DXd, FDA review of the patient narrative could not rule out ILD/pneumonitis as the cause of death.

Overall, the risk of ILD/pneumonitis appears lower with T-DXd 5.4 mg/kg than with T-DXd 6.4 mg/kg based on the results of Study U206 and support the recommendation of the lower dose for treatment of patients with *HER2*-mutant NSCLC. The risk of ILD/pneumonitis with T-DXd 5.4 mg/kg is adequately addressed through a boxed warning in product labeling.

8.2.5.2 Left Ventricular Dysfunction

The Applicant’s Presentation of Data:

Of the 13 relevant PTs for the AESI of LV dysfunction, only the PT of ejection fraction decreased was reported in the *HER2*-mutant NSCLC T-DXd 6.4 mg/kg Pool (5 [4.9%] subjects). All events were nonserious, 1 event was Grade 1, 3 were Grade 2, and 1 was Grade 3.

Measurements of LVEF from laboratory data (every 4 cycles) were graded per CTCAE version 5.0, with each LVEF measurement assigned a CTCAE grade. Using these criteria, 14.6% of subjects in the *HER2*-mutant NSCLC T-DXd 6.4 mg/kg Pool had a post-baseline LVEF value that met the laboratory criteria for a Grade 2 LVEF decrease and 3.4% met the criteria for a Grade 3 LVEF decrease. No subject had a post-baseline resting LVEF of <20%.

The Applicant’s Position:

Available data suggest that T-DXd is not associated with a risk of LV dysfunction. Since LVEF decrease and congestive heart failure have been reported for drugs in a similar class, and considering the limited long-term exposure data in the target population, LV dysfunction remains an important potential risk, and should be monitored regularly during treatment and managed as clinically indicated.

In clinical trials of T-DXd across multiple tumor types and doses, the overall safety profile of T-DXd is consistent and there is no notable difference observed for the risk of LV dysfunction. For the prescriber, the management of this AE is the same irrespective of the tumor type or dose. Based on this assessment and to provide a more precise numerical estimate of this AE in the T-DXd-treated patient population, the Applicant has proposed (b) (4) is presented for LV dysfunction in the Warnings and Precautions of the USPI.

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The FDA's Assessment:

FDA agrees with the Applicant's assessment. In Study U206 one (1.0%) patient in the T-DXd 5.4 mg/kg arm and no patients in the T-DXd 6.4 mg/kg dose group had left ventricular (LV) dysfunction. The single event in the T-DXd 5.4 mg/kg arm was recorded as CTCAE Grade 1. In the primary safety population (T-DXd 5.4 mg/kg arm of Study U206) five patients (1%) experienced a 10% to 19% decrease from baseline in left ventricular ejection fraction (LVEF) to minimum post-treatment value and no patients experienced a ≥20% decrease from baseline in LVEF to minimum post-treatment value. The risk of LV dysfunction appears consistent with known risks of T-DXd and is adequately addressed through product labeling.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Presentation of Data:

None.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Presentation of Data:

Subgroup evaluations of TEAEs were conducted to identify potential safety issues in particular subpopulations defined by intrinsic factors (age, sex, ECOG PS, renal and hepatic functions) and extrinsic factors (country, geographic region), as well as prior anticancer therapy. Notable findings in the HER2-mutant NSCLC T-DXd 6.4 mg/kg Pool were as follows:

Age: a higher proportion of subjects aged ≥65 years had SAEs and TEAEs associated with study drug discontinuation and a higher proportion of subjects aged <65 years had TEAEs associated with dose reduction (overall and drug-related) and drug-related ≥Grade 3 TEAEs.

Sex: a higher proportion of female subjects with drug-related TEAEs ≥Grade 3 and a higher proportion of male subjects with TEAEs associated with study drug interruption.

ECOG PS: a lower proportion of subjects with ECOG PS 0 had TEAEs ≥Grade 3, TEAEs associated with an outcome of death, and SAEs (overall and drug related) and a higher proportion of subjects with ECOG PS 0 had TEAEs associated with dose reduction (overall and drug related) and TEAEs associated with study drug interruption.

Renal function at baseline: no consistent pattern. SAEs, ≥Grade 3 TEAEs, and adjudicated drug-related ILD (any grade) were reported in a higher proportion of subjects and TEAEs associated with study drug discontinuation and/or dose reduction in a lower proportion of subjects with mild and/or moderate renal impairment than subjects with normal renal function.

Hepatic function at baseline: no consistent pattern.

Country: a lower proportion of subjects from Japan had SAEs and a higher proportion of subjects from

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Japan had ≥Grade 3 TEAEs (overall and drug-related), TEAEs associated with study drug interruption (overall and drug related), TEAEs associated with dose reduction (overall and drug related), and drug related TEAEs associated with study drug discontinuation.

Geographic region: a higher proportion of subjects from Asia had TEAEs for most parameters that subjects from Europe or North America, with exception of SAEs and TEAEs associated with an outcome of death that were observed in a higher proportion of subjects from Europe.

Prior anticancer therapy: a higher proportion of subjects who received prior PD-1/PD-L1 inhibitors had drug related TEAEs associated with study drug interruption.

The Applicant's Position:

TEAEs with a notable (i.e., ≥10 percentage points) difference were observed in certain subgroups. Regardless of the subgroup, TEAEs were generally manageable with dose modification and routine clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that TEAEs were not significantly different among subgroups. Safety analyses by subgroups in Study U206 did not reveal significant differences among key demographic factors including renal function at baseline, geographic region, and prior anti-cancer therapies.

8.2.8 Specific Safety Studies/Clinical Trials

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

A total of 19 (18.6%) of the 102 HER2-mutant NSCLC subjects were treated with T-DXd at 6.4 mg/kg for more than 1 year.

Within the MedDRA system organ class of Neoplasms Benign, Malignant and Unspecified, the following PT was reported: tumor associated fever (1/102 [1.0%] subject). The event was Grade 1, nonserious, considered unrelated to study drug by the investigator, and required no dose modification. The event was not resolved at the time of the DCO.

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The Applicant's Position:

TEAEs primarily related to underlying disease have been reported at a low frequency in the MedDRA system organ class of Neoplasm Benign, Malignant and Unspecified; however, carcinogenicity studies have not been conducted and limited long-term data preclude definitive evaluation of carcinogenicity.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that no new information is provided in the current sBLA submission. Although no new neoplasms were reported in Study U206 per MedDRA classification, specific carcinogenicity studies have not been performed. Given the serious, life-threatening context of the current indication, and the lack of prior reports of new tumor development, this approach appears acceptable.

Human Reproduction and Pregnancy

The Applicant's Presentation of Data

Based on the composition and mechanism of action of the product, as well as data from similar products of the same class, teratogenic potential cannot be excluded. In postmarketing reports, use of trastuzumab, a HER2-receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and the T-DXd mechanism of action, the topoisomerase I inhibitor component of T-DXd can also cause embryo-fetal harm when administered to a pregnant woman. T-DXd should not be administered to pregnant women, women attempting to conceive, or women who are breastfeeding.

Based on results from animal toxicity studies, T-DXd may impair male reproductive function and fertility.

The Applicant's Position:

Based on composition and mechanism of action of the product, as well as data from similar products of the same class, teratogenic potential cannot be excluded.

The FDA's Assessment:

FDA agrees with the Applicant's position. No new relevant clinical data were available from Study U206.

Pediatrics and Assessment of Effects on Growth

The Applicant's Presentation of Data:

Lung cancer is extremely rare in the pediatric population.

The Applicant's Position:

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A full waiver from pediatric study requirements for T-DXd in the treatment of HER2-mutant NSCLC is applicable, because studies are impossible or highly impractical to conduct.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Presentation of Data:

There were no cases of overdose in NSCLC subjects with HER2 mutation. No studies have been conducted that assess withdrawal or rebound effects of T-DXd.

The Applicant's Position:

In the event of overdose, subjects should be observed, and appropriate supportive care should be given, if required. Given the nature of T-DXd and its IV administration, no abuse or dependence is anticipated. Given the disease being treated and the nature of T-DXd, no withdrawal or rebound effects are anticipated.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. In addition to the studies reported here by the Applicant, there were no cases of overdose in Study U206.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Presentation of Data:

Since the first approval of T-DXd on 20 Dec 2019 in the U.S., the estimated cumulative postmarketing patient exposure through 01 Dec 2021 (latest available data) was (b) (4) patient years.

The first 3 Periodic Benefit Risk Evaluation Reports covered the reporting periods 20 Dec 2019 through 19 Jun 2020, 20 Jun 2020 through 19 Dec 2020, and 20 Dec 2020 through 19 Jun 2021. There were no new safety findings based on spontaneous cases identified during these prior periods. For the purpose of this application, a periodic output of spontaneous reports was generated from the global safety database from 20 Jun 2021 through 01 Dec 2021. For this period, 2934 AEs were reported during the post-marketing period, the majority of which (2275) were nonserious. Reported events were generally consistent with the known safety profile of T-DXd. There were no new safety findings identified during this period.

The Applicant's Position:

Review of spontaneous postmarketing events during this period did not reveal any new safety information that would impact the overall benefit-risk profile of ENHERTU. The reported events were generally consistent with the known safety profile of T-DXd.

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The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Presentation of Data:

None.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.2.11 Integrated Assessment of Safety

The Applicant's Presentation of Data:

The overall safety profile of T-DXd was evaluated in the target population of subjects with HER2-mutant NSCLC treated with T-DXd 6.4 mg/kg as well as across different tumor types and the 5.4 mg/kg dose. No new safety signals were identified.

The Applicant's Position:

The safety profile in HER2-mutant NSCLC is generally consistent with the known safety profile of T-DXd. TEAEs were generally manageable by dose modifications and routine clinical practice. ILD/pneumonitis is an important identified risk of T-DXd. The majority of the reported cases of ILD were either Grade 1 or Grade 2 and were manageable by following clinical treatment guidelines. T-DXd demonstrated an acceptable safety profile in the target population.

The FDA's Assessment:

FDA disagrees with the Applicant's assessment. The incidence of ILD/pneumonitis with T-DXd 6.4 mg/kg (14-26%) was greater in the NSCLC population than in previously-approved tumor histologies (T-DXd 5.4 mg/kg for metastatic breast cancer and T-DXd 6.4 mg/kg for gastric cancer). The incidence of ILD/pneumonitis with T-DXd 5.4 mg/kg (6%) for patients with HER2-mutant NSCLC is consistent with the risk identified across other tumor types. This risk of ILD/pneumonitis with T-DXd 5.4 mg/kg in HER2-mutant NSCLC is acceptable in the context of this serious and life-threatening disease. As ILD/pneumonitis currently has a boxed warning and no new safety signals were identified, FDA considers the current product labeling adequate to address safety concerns.

SUMMARY AND CONCLUSIONS

8.3 STATISTICAL ISSUES

The FDA's Assessment:

There were no major statistical issues in the review of this application. The primary efficacy evaluation was based on the interim data from the prespecified early cohort of 52 patients with *HER2*-mutant NSCLC treated with T-DXd 5.4 mg/kg in Study U206. During review of this sBLA, the Applicant submitted efficacy data from two interim analyses. The first DCO date was March 24, 2022, at which time those 52 patients had been followed for at least 4.5 months after initiation of study treatment. Per FDA's request, the Applicant submitted updated data with an additional 90 days of follow-up with a DCO date of June 22, 2022, to allow for a more precise estimation of response rate and to provide some initial information regarding duration of response. The Applicant updated efficacy results with respect to ORR and DOR for the 52 patients treated with T-DXd 5.4 mg/kg in the prespecified early cohort.

Due to the single-arm setting of the supportive studies, FDA considers time-to-event endpoints, such as PFS and OS to be uninterpretable and are considered descriptive only. Additionally, results from subgroup analyses are considered exploratory and should be interpreted with caution, particularly those with small sample sizes.

Due to the limited number of patients treated with T-DXd 6.4 mg/kg in Study U206 and Study J101, the efficacy results for the 6.4 mg/kg dose from these studies should be interpreted with caution.

8.4 CONCLUSIONS AND RECOMMENDATIONS

The FDA's Assessment:

Daiichi Sankyo has provided substantial evidence of effectiveness supporting the accelerated approval of T-DXd under 21 CFR part 314 subpart H, for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

The current application is supported by the results of Study U206 (DESTINY-Lung02) and Study U204 (DESTINY-Lung01). Study U206 was an international, multi-center, randomized, dose-optimization trial comparing T-DXd 5.4 mg/kg and 6.4 mg/kg by intravenous infusion every 3 weeks that enrolled 102 patients at the 5.4 mg/kg dose level and 50 patients at the 6.4 mg/kg dose level. Study U204 was an international, multi-center, single-arm trial that enrolled 91 patients with NSCLC with *HER2* mutations and had received prior systemic therapy. Patients received T-DXd 6.4 mg/kg by intravenous infusion

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every 3 weeks. The primary endpoint of these trials was overall response rate (ORR) by blinded independent central review.

The primary efficacy population included a prespecified early analysis of 52 patients in the 5.4 mg/kg arm of Study U206 with at least 4.5 months follow-up, which allows for three imaging assessments. At the March 24, 2022 DCO, the confirmed ORR was 53.8% (95% CI: 39.5, 67.8) and the median DOR was not reached. This efficacy result was consistent with the confirmed ORR among 28 patients treated at the 6.4 mg/kg dose level in Study U206 (42.9% [95% CI: 24.5, 62.8]) and 91 patients treated at the 6.4 mg/kg dose level in Study U204 (54.9% [95% CI: 44.2, 65.4]). Data after an additional 90 days of follow-up were provided for the primary efficacy population demonstrating an ORR of 57.7% (95% CI: 43.2, 71.3) with a median DOR of 8.7 months (95% CI: 7.1, NE).

T-DXd has an acceptable safety profile for the intended population of patients with *HER2*-mutant NSCLC who have a life-threatening disease. The safety review focused on the 101 patients treated at the 5.4 mg/kg dose level in Study U206 and was supported by data from patients treated at the 6.4 mg/kg dose level in Study U206, Study U204, and Study J101. ILD and pneumonitis were evaluated by a blinded independent review committee. No new safety signals were identified during the course of this review. The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia. ILD/pneumonitis was more frequent in the cohorts of patients treated at the 6.4 mg/kg dose level (14-26%) than the cohort treated at the 5.4 mg/kg dose level (6%). Based on consistent efficacy and reduced toxicity compared to the 6.4 mg/kg dose, the review division recommends approval of the 5.4 mg/kg dose administered every 3 weeks.

Given the size of the efficacy population, the duration of follow-up, and the single-arm nature of the primary efficacy population, we recommend accelerated approval for this application. (b) (4)

These ongoing studies allow for multiple pathways to verify the clinical benefit of T-DXd in patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations and who have received a prior systemic therapy.

Based on a favorable benefit-risk assessment, FDA recommends accelerated approval for T-DXd for the following indication:

The treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC)

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whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

Based on dose-optimization results, the recommended dose for this indication is:

5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

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9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

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10 PEDIATRICS

The Applicant's Position:

Pediatric studies of T-DXd for the treatment of HER2-mutant NSCLC are impossible or highly impracticable to conduct as the condition is not reported to occur in the pediatric population.

The FDA's Assessment:

FDA agrees with the Applicant's position given the lack of reported cases of *HER2*-mutant NSCLC in pediatric patients.

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11 LABELING RECOMMENDATIONS

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Prescribing Information		
Highlights	Updated to reflect changes made to the Full Prescribing Information.	Most common adverse reactions were updated.
1 Indications and Usage	New indication for HER2-mutant NSCLC added with accelerated approval statement, based on DESTINY-Lung01.	Indication statement refined to include the description "activating" <i>HER2</i> mutations.
2.1 Patient Selection	New patient selection section and text added for NSCLC	FDA revised subheadings for clarity.
2.3 Recommended Dosage and Schedules	Recommended dosage added for NSCLC	FDA moved administration instructions to under the administration subheading.
2.4 Dose Modifications	Added NSCLC to Table 1: Dose Reduction Schedule	Cross references to Section 5 were added to the dosage modification table.
5.1 Warnings and Precautions, Interstitial Lung Disease/Pneumonitis	(b) (4)	FDA revised (b) (4) for clarity.
5.2 Neutropenia	(b) (4)	FDA revised (b) (4) for

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	(b) (4)	clarity.
5.3 Left Ventricular Dysfunction	(b) (4)	FDA revised (b) (4) for clarity.
6.1 (b) (4)	(b) (4) Added new subsection for HER2-mutant NSCLC ADR data (6.4 mg/kg pool from DESTINY-Lung01 and Study J101).	FDA revised (b) (4) The subsection for <i>HER2</i> -mutant NSCLC was reviewed for accuracy and text revised for brevity and clarity.
6.2 Immunogenicity	Updated data to include patients with NSCLC.	For consistency with the draft guidance <i>Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling Content and Format</i> , this section was moved to 12.6.
8.5 Geriatric Use	Added outcomes from DESTINY-Lung01 and Study J101 for patients ≥65 years of age compared to younger patients.	Text revised for consistency with 21 CFR 201.57(c)(9)(v).
8.6 Renal impairment	(b) (4)	Text revised for consistency

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	(b) (4)	with current labeling practice.
12.3 Pharmacokinetics	Clarified exposure statement. Added new paragraph for HER2-mutant NSCLC. Updated distribution value. Updated elimination half-life and clearance values. Updated Specific Populations statement.	FDA reviewed the pharmacokinetics subsection for accuracy and text revised for brevity and clarity.
14 Clinical Studies	Added efficacy information from DESTINY-Lung01 in a new subsection.	The Clinical Studies subsection was reviewed for accuracy and the text revised for brevity and clarity.
Medication Guide		
What is ENHERTU	Added a bullet to new indication for lung cancer.	FDA reviewed and revised the Medication Guide for consistency with the labeling.
What are the possible side effects of ENHERTU	Most common side effects added for lung cancer	FDA reviewed and revised the Medication Guide for consistency with the labeling.

The Applicant's Position:

Based on the results from Studies U204 and J101, the Applicant proposes the significant changes described in the table above for the ENHERTU Prescribing Information and Medication Guide. The proposed changes for ENHERTU labeling reflect changes from the version approved on 15 Jan 2021.

The FDA's Assessment:

The proposed prescribing information has been edited in accordance with 21 Code of Federal Regulations (CFR) and final and draft labeling Guidances to ensure safe and effective use of ENHERTU. The prescribing information has been updated to include results from Study U206.

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12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

The risks of T-DXd are acceptable in the indicated population with a serious and life-threatening condition. The safe use of T-DXd can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

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13 POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

The following post marketing requirements will be issued for this application:

PMR #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 activating *HER2* (*ERBB2*) mutations 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 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

PMR #1 Rationale

The accelerated approval of fam-trastuzumab deruxtecan-nxki was based on an interim analysis of single-arm data from a randomized dose-optimization study with a primary endpoint of overall response rate (ORR). In the context of the limited patient numbers and follow-up in the interim analysis, this PMR will provide greater precision around the point estimate for ORR that may verify the clinical benefit of fam-trastuzumab deruxtecan-nxki in patients with unresectable or metastatic *HER2*-mutant non-small cell lung cancer who have received prior systemic therapy.

PMR #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.

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Final Protocol Submission: 07/2021 (completed)

Study Completion: 03/2028

Final Report Submission: 09/2028

PMR #2 Rationale

The accelerated approval of fam-trastuzumab deruxtecan-nxki was based on an interim analysis of single-arm data from a randomized dose-optimization study with a primary endpoint of overall response rate. This PMR will provide overall survival results from an ongoing randomized study in the first-line setting that may verify the clinical benefit of fam-trastuzumab deruxtecan-nxki in patients with unresectable or metastatic *HER2*-mutant non-small cell lung cancer who have received prior systemic therapy.

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14 DIVISION DIRECTOR (DHOT) (NME ONLY)

X

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15 DIVISION DIRECTOR (OCP)

X

Enhertu® (fam-trastuzumab deruxtecan-nxki)

16 DIVISION DIRECTOR (OB)

X

Enhertu® (fam-trastuzumab deruxtecan-nxki)

17 DIVISION DIRECTOR (CLINICAL)

X

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18 OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 APPENDICES

19.1 REFERENCES

The Applicant's References:

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19.2 FINANCIAL DISCLOSURE

The Applicant's Position:

The Applicant provided financial disclosure information for clinical investigators involved in the covered clinical Study DS8201-A-U204. One investigator had disclosable financial interests or arrangements under the significant payments of other sorts of financial disclosure category. No concerns were raised regarding the overall integrity of the study data.

Despite the Applicant's due diligence attempting to obtain the information, the Applicant was unable to obtain financial disclosure information for 5 investigators for Study U204. The Applicant has not made any significant payments of other sorts to these investigators.

The FDA's Assessment:

The Applicant's assessment above is based on Study U204. FDA agrees with that assessment; however, as Study U206 was the primary trial used to support the current approval, the financial disclosures for the covered clinical study are listed below.

Covered Clinical Study (Name and/or Number):* DS8201-A-U206 (DESTINY-Lung02)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>500</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be		

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influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Data:

Not applicable

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

19.4 OCP APPENDICES (TECHNICAL DOCUMENTS SUPPORTING OCP RECOMMENDATIONS)

19.4.1 Population PK Analysis

Executive Summary

The FDA's Assessment:

In support of the proposed dosing regimen of 5.4 mg/kg Q3W of Trastuzumab deruxtecan (T-DXd) in patients with *HER-2* mutant NSCLC, the applicant submitted topline results for updated population

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pharmacokinetic (PPK) report in the briefing documents (see section *PPK Review Issues*). The population PK analysis was updated from the previous PK model of T-DXd by including both the PK data collected from subjects with NSCLC in Study U206 (from interim analysis with data cut off date 24 Mar 2022) and the previous PK datasets (see section *PPK Assessment Summary*).

The PK of T-DXd was described by a two-compartment model with linear clearance. And the PK of DXd was characterized by a one-compartment model with linear clearance and time varying production from the T-DXd. The final popPK model for T-DXd and DXd was well validated and the updated PPK model is generally in line with previous model (see section *PPK Assessment Summary*).

The covariate analyses showed there were no clinically significant differences in the PK of T-DXd and DXd based on body weight, age, sex, race, creatinine clearance, target tumor size, varying degrees of organ dysfunctions including mild to moderate renal impairment, and mild to moderate hepatic impairment. The addition of data from Study U206 did not change the overall conclusions of the population PK analysis for subjects with NSCLC.

In general, the applicant's population PK analysis for T-DXd and DXd is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the developed model was acceptable to be used to derive exposure metrics for exposure response analysis, and to support applicant's proposed labeling statements about general PK information including intrinsic and extrinsic factors in the current submission.

PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	Update an established PopPK model for both the intact ADC (T-DXd) and the payload (DXd) with data from Study U204 Assess the impact of potential covariates on the PK of T-DXd and DXd, with a focus on covariates that may differ between cancer types Estimate individual post hoc PK parameters for use in subsequent ER analyses Compare exposures among subpopulations of interest, including by cancer type, sex, race-country, region and HER2 status
Study Included	J101, J102, A103, A104, U201, J202, U205, and U204

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Dose(s) Included		0.8, 1.6, 3.2, 5.4, 6.4, 7.4, and 8.0 mg/kg
Population Included		BC, gastric/GEJ cancer, NSCLC, other cancers
Population Characteristics (Applicant - Table)	General	Age: median 60 yrs (range: 20.0-96.0) Weight: median 59.6 kg (range: 27.3-125) Sex: 344 (32.5%) male, 715 (67.5%) female Race: 379 (35.8%) White, 21 (2.0%) Black or African American, 611 (57.7%) Asian, 42 (4.0%) Other, 6 (0.6%) Missing Cancer type: 512 (48.3%) BC, 293 (27.7%) gastric/GEJ, 199 (18.8%) NSCLC, 55 (5.2%) other cancers
	Organ Impairment	Hepatic (NCI): 67.4% normal function, 31.7% mild impairment, 4% moderate impairment, and 0.5% missing Renal (CrCL using Cockcroft-Gault equation): 41.3% normal function, 41.1% mild impairment, 17.4% moderate impairment, and 0.3% severe impairment
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		No. of patients: 1059 No. of PK samples: 16,622 T-DXd, and 16,715 DXd T-DXd 5.3% of pre-dose BLQ, 0.5% of post-dose BLQ DXd 5.3% of pre-dose BLQ, 0.2% of post-dose BLQ <i>Note: BLQ % values are based on all PK samples in the dataset</i>
Sampling Schedule	Rich Sampling	<u>J101</u> : Prior to and after the infusion for Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 h after start of infusion on Cycle 1; on Days 2, 4, 8, and 15 of Cycle 1; and on Days 8 and 15 of Cycle 3. For the dose-escalation phase, an additional PK sample at 4 h from the start of infusion was collected on Cycle 3. <u>U201</u> : Prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 h after start of infusion on Cycle 1; on Days 8 and 15 of Cycle 1; and at 4 and 7 h after the start of infusion on Cycle 3. For PK stage of Part 1, additional PK sampling at Days 2 and 4 of Cycle 1.

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		<u>J102 and A103</u>: Same as PK stage of Part 1 for Study U201 PK; additional sampling points at 2 h after the start of infusion and Days 2, 4, 8, and 15 of Cycle 3. <u>A104</u>: Prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 h after the start of infusion on Cycles 2 and 3; and at Days 2, 4, 8, 12, and 17 of Cycles 2 and 3. <u>J202</u>: Prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; and at 4 and 7 h after the start of infusion on Cycles 1 and 3. <u>U204</u>: Prior to and after the infusion on Cycles 1, 2, 3, 4 and 6; at 5 h after the start of infusion on Cycle 1; and at Days 8 and 15 of Cycle 1. <u>U205</u>: Prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; at 5 h after the start of infusion on Cycle 1; and at Days 8 and 15 of Cycle 1.
	In ITT Population	Prior to and after the infusion on Cycles 1, 2, 3, 4, 6, and 8; and at 5 h after the start of infusion on Cycle 1.
Covariates Evaluated	Static	<u>T-DXd</u>: cancer type, race, region, hepatic impairment (NCI), CrCL, ECOG PS, total gastrectomy, line of therapy, HER2 status, ADA. <u>DXd</u>: Sex, cancer type, race, region, CrCL, race-country, line of therapy.
	Time-varying	<u>None</u>
Final Model		Summary Acceptability [FDA's comments]
Software and Version		NONMEM® (version 7.4.3)
Model Structure		<u>T-DXd</u>: a 2-compartment model with linear elimination <u>DXd</u>: 1-compartment model with a 2-component, time-varying release rate from T-DXd
Model Parameter Estimates		Applicant - Table ; Applicant - Table
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Parameters were generally estimated with good precision (RSE <20%) except for race-country (Japan) effect on $V_{2,T-DXd}$, the FL-DP1

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	formulation on V_{DXd}, and other cancer (not BC, GC, NSCLC) on CL_{DXd} and V_{DXd}. For T-DXd, the between-subject variability in CL_{T-DXd} and $V_{1,T-DXd}$ was 24.4% and 15.0%, respectively. For DXd, the between-subject variability in CL_{DXd}, V_{DXd}, K_{rel}, and FPC1 was 25.3%, 39.7%, 35.7%, and 25.6%, respectively. The shrinkage for T-DXd parameters was approximately 7% to 32% and DXd parameters was approximately 18% to 38%.	
BLQ for Parameter Accuracy	PK observations BLQ were retained in the dataset and were flagged as missing. As up to 0.5% of post-dose observations were BLQ for both T-DXd and DXd, likelihood-based approaches were not necessary and were not used to handle BLQ observations.	
GOF, VPC	Applicant - Figure 10; Applicant - Figure 11; Applicant - Figure 12	
Significant Covariates and Clinical Relevance	Applicant - Figure 13; Applicant - Figure 14	
Analysis Based on Simulation (optional)	Not applicable.	
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	Revised information to include data from NSCLC subjects.	

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Applicant - Table 34: Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

Covariate Category	Count (%)								
	Study J101 (N=286)	Study J102 (N=51)	Study A103 (N=12)	Study A104 (N=40)	Study U201 (N=250)	Study J202 (N=169)	Study U205 (N=76)	Study U204 (N=175)	Overall (N=1059)
Sex									
Male	62 (21.7)	0 (0)	0 (0)	18 (45.0)	0 (0)	128 (75.7)	55 (72.4)	81 (46.3)	344 (32.5)
Female	224 (78.3)	51 (100)	12 (100)	22 (55.0)	250 (100)	41 (24.3)	21 (27.6)	94 (53.7)	715 (67.5)
Race									
White	80 (28.0)	0 (0)	0 (0)	0 (0)	132 (52.8)	0 (0)	67 (88.2)	100 (57.1)	379 (35.8)
Black/African American	8 (2.80)	0 (0)	0 (0)	0 (0)	5 (2.00)	0 (0)	1 (1.32)	7 (4.00)	21 (1.98)
Asian	190 (66.4)	51 (100)	12 (100)	40 (100)	101 (40.4)	169 (100)	3 (3.95)	45 (25.7)	611 (57.7)
Other	8 (2.80)	0 (0)	0 (0)	0 (0)	7 (2.80)	0 (0)	4 (5.26)	23 (13.1)	42 (3.97)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	5 (2.00)	0 (0)	1 (1.32)	0 (0)	6 (0.567)
Race-Country									
Asian from Japan	177 (61.9)	51 (100)	0 (0)	31 (77.5)	53 (21.2)	134 (79.3)	0 (0)	36 (20.6)	482 (45.5)
Asian not from Japan	14 (4.90)	0 (0)	12 (100)	9 (22.5)	49 (19.6)	35 (20.7)	3 (3.95)	9 (5.14)	131 (12.4)
Non-Asian	95 (33.2)	0 (0)	0 (0)	0 (0)	148 (59.2)	0 (0)	73 (96.1)	130 (74.3)	446 (42.1)
Region									
Asia	177 (61.9)	51 (100)	12 (100)	40 (100)	93 (37.2)	169 (100)	0 (0)	36 (20.6)	578 (54.6)
North America	109 (38.1)	0 (0)	0 (0)	0 (0)	77 (30.8)	0 (0)	33 (43.4)	65 (37.1)	284 (26.8)
Europe	0 (0)	0 (0)	0 (0)	0 (0)	80 (32.0)	0 (0)	43 (56.6)	74 (42.3)	197 (18.6)
Hepatic function									
Normal	169 (59.1)	28 (54.9)	9 (75.0)	30 (75.0)	141 (56.4)	114 (67.5)	64 (84.2)	159 (90.9)	714 (67.4)
Mild impairment	117 (40.9)	23 (45.1)	3 (25.0)	10 (25.0)	104 (41.6)	53 (31.4)	11 (14.5)	15 (8.57)	336 (31.7)
Moderate impairment	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.800)	2 (1.18)	0 (0)	0 (0)	4 (0.378)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.20)	0 (0)	1 (1.32)	1 (0.571)	5 (0.472)

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Covariate Category	Count (%)								
	Study J101 (N=286)	Study J102 (N=51)	Study A103 (N=12)	Study A104 (N=40)	Study U201 (N=250)	Study J202 (N=169)	Study U205 (N=76)	Study U204 (N=175)	Overall (N=1059)
Renal function									
Normal	125 (43.7)	23 (45.1)	5 (41.7)	19 (47.5)	121 (48.4)	48 (28.4)	36 (47.4)	60 (34.3)	437 (41.3)
Mild impairment	119 (41.6)	23 (45.1)	7 (58.3)	17 (42.5)	96 (38.4)	72 (42.6)	28 (36.8)	73 (41.7)	435 (41.1)
Moderate impairment	41 (14.3)	5 (9.80)	0 (0)	4 (10.0)	33 (13.2)	49 (29.0)	12 (15.8)	40 (22.9)	184 (17.4)
Severe impairment	1 (0.350)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.14)	3 (0.283)
Cancer type									
Breast	182 (63.6)	51 (100)	12 (100)	17 (42.5)	250 (100)	0 (0)	0 (0)	0 (0)	512 (48.3)
Gastric/GEJ	47.0 (16.4)	0 (0)	0 (0)	1 (2.50)	0 (0)	169 (100)	76 (100)	0 (0)	293 (27.7)
NSCLC	18.0 (6.29)	0 (0)	0 (0)	6 (15.0)	0 (0)	0 (0)	0 (0)	175 (100)	199 (18.8)
Other	19 (6.64)	0 (0)	0 (0)	15 (37.5)	0 (0)	0 (0)	0 (0)	0 (0)	55 (5.19)
HER2 status									
Negative	67 (23.4)	47 (92.2)	0 (0)	8 (20.0)	1 (0.400)	44 (26.0)	0 (0)	0 (0)	167 (15.8)
Positive	184 (64.3)	4 (7.84)	12.0 (100)	23 (57.5)	249 (99.6)	123 (72.8)	75 (98.7)	0 (0)	670 (63.3)
Mutant	11 (3.85)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	88 (50.3)	99 (9.35)
Overexpressing	7 (0.699)	0 (0)	0 (0)	6 (15.0)	0 (0)	0 (0)	0 (0)	87 (49.7)	100 (9.44)
Missing	17 (5.94)	0 (0)	0 (0)	3 (7.50)	0 (0)	2 (1.20)	1 (1.32)	0 (0)	23 (2.17)
ECOG PS									
0	177 (61.9)	31 (60.8)	3 (25.0)	21 (52.5)	143 (57.2)	83 (49.1)	27 (35.5)	41 (23.4)	526 (49.7)
1	109 (38.1)	20 (39.2)	9 (75.0)	19 (47.5)	106 (42.4)	86 (50.9)	49 (64.5)	134 (76.6)	532 (50.2)
2	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.400)	0 (0)	0 (0)	0 (0)	1 (0.0944)
Prior HER2 therapy									
No	85 (29.7)	39 (76.5)	0 (0)	16 (40.0)	0 (0)	42 (24.9)	0 (0)	170 (97.1)	352 (33.2)
Yes	201 (70.3)	12 (23.5)	12 (100)	24 (60.0)	250 (100)	127 (75.1)	76 (100)	5 (2.86)	707 (66.8)
T-DXd formulation									
FL-DP1	265 (92.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	265 (25.0)
FL-DP2	21.0 (7.34)	0 (0)	0 (0)	0 (0)	142 (56.8)	0 (0)	0 (0)	0 (0)	163 (15.4)

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Covariate Category	Count (%)								
	Study J101 (N=286)	Study J102 (N=51)	Study A103 (N=12)	Study A104 (N=40)	Study U201 (N=250)	Study J202 (N=169)	Study U205 (N=76)	Study U204 (N=175)	Overall (N=1059)
Lyo-DP	0 (0)	51 (100)	12 (100)	40 (100)	108 (43.2)	169 (100)	76 (100)	175 (100)	631 (59.6)
Total gastrectomy									
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	32 (18.9)	0 (0)	0 (0)	32 (3.02)
No	239 (83.6)	51 (100)	12 (100)	39 (97.5)	250 (100)	137 (81.1)	76 (100)	175 (100)	979 (92.4)
Missing	47 (16.4)	0 (0)	0 (0)	1 (2.50)	0 (0)	0 (0)	0 (0)	0 (0)	48 (4.53)
ADA status									
Yes	5 (1.75)	3 (5.88)	0 (0)	1 (2.50)	15 (6.00)	24 (14.2)	7 (9.21)	20 (11.4)	75 (7.08)
No	281 (98.3)	48 (94.1)	12 (100)	39 (97.5)	235 (94.0)	145 (85.8)	69 (90.8)	155 (88.6)	984 (92.9)
Line of therapy									
2 nd	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	76 (100)	175 (100)	251 (23.7)
3 rd	286 (100)	51 (100)	12 (100)	40 (100)	250 (100)	169 (100)	0 (0)	0 (0)	808 (76.3)

Notes: Per study percentage for each category was computed by dividing with the study total; overall percentage per category was computed by dividing with the total number of subjects included in the analysis (N=). Percentages below 0.5% are presented with a zero percentage value. Source: Population PK report.

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Applicant - Table 35: Parameter Estimates and SE from Final Population PK Model (T-DXd)

Parameter	Final T-DXd Model (run369)				
	Estimate		Between-subject Variability		
	Typical Value	RSE (%)	Magnitude(%CV)	RSE (%)	Shrinkage (%)
Clearance (CL _{T-DXd} , L/d)	0.418	1.32	24.4	2.53	6.69
Central volume of distribution (V _{1,T-DXd} , L)	2.75	0.646	15.0	2.61	6.64
Distributional clearance (Q _{T-DXd} , L/d)	0.208	1.31	28.4	4.59	32.1
Peripheral volume of distribution (V _{2,T-DXd} , L)	4.94	4.04	77.2	3.94	22.8
Albumin (g/L) on CL _{T-DXd}	-0.551	9.74	-	-	-
Race-Country (Japan) on CL _{T-DXd}	-0.0941	15.4	-	-	-
Tumor size (mm) on CL _{T-DXd}	0.0654	15.9	-	-	-
Body weight (kg) on CL _{T-DXd}	0.451	8.67	-	-	-
GC on CL _{T-DXd}	0.165	14.5	-	-	-
NSCLC and other cancer (not BC or GC) on CL _{T-DXd}	0.113	18.3	-	-	-
Male effect on V _{1,T-DXd}	0.108	12.7	-	-	-
Body weight (kg) on V _{1,T-DXd}	0.467	5.29	-	-	-
GC on V _{1,T-DXd}	0.0823	17.4	-	-	-
Race-Country (Japan) on V _{2,T-DXd}	-0.134	30.9	-	-	-
Residual unexplained variability					
Proportional residual error SD	0.153	0.346	-	-	-
Additive residual error SD (ng/mL)	1222	2.14	-	-	-
Covariance of CL _{T-DXd} and V _{1,T-DXd}	0.0191	3.82	-	-	-

Notes: RSE of parameter estimate are calculated as $100 \times (\text{SE}/\text{typical value})$; RSE of between-subject variability magnitude are calculated as $100 \times (\text{SE}/\text{variance estimate})/2$. CV% for the between-subject variability estimates are based on the estimated variances. Shrinkage (%) is calculated as $100 \times (1 - \text{SD}(\text{ETA})/\sqrt{\text{variance}})$. Overall residual unexplained variability shrinkage was estimated to be 8.93. The correlation coefficient between CL_{T-DXd} and V_{1,T-DXd} was estimated as 0.535.

Source: Population PK report.

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Applicant - Table 36: Parameter Estimates and SE from Final Population PK Model (DXd)

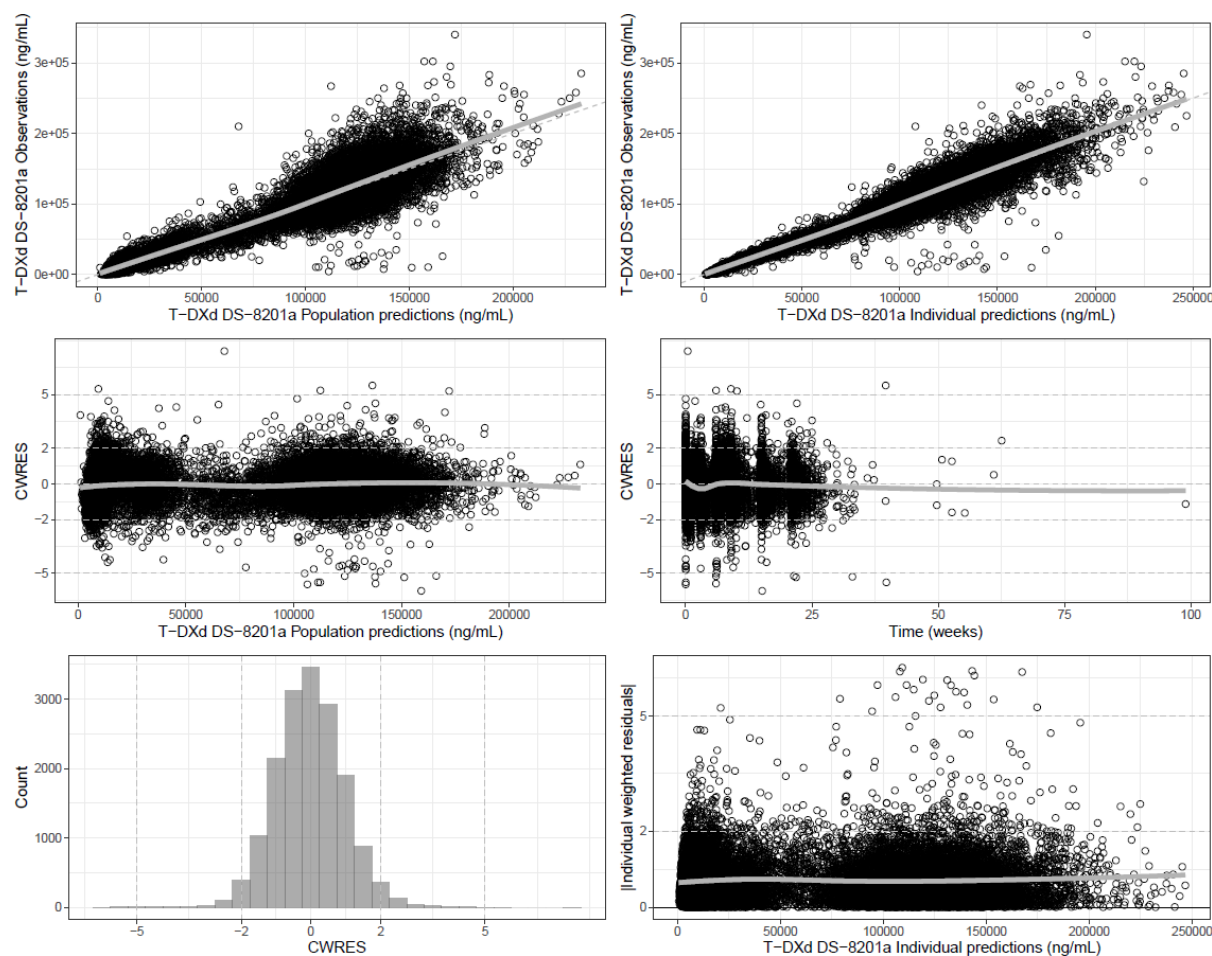
Parameter	T-DXd Base Model (run619)					Typical Value Estimate Previous Analysis without Study U204
	Estimate		Between-subject Variability			
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)	
DXd clearance (CL _{DXd} , L/h)	18.3	3.56	25.3	5.17	37.8	18.5 (3.78)
DXd volume of distribution (V _{DXd} , L)	Fixed 17*BSA	-	39.7	3.87	25.0	Fixed 17*BSA
Release rate (K _{rel} , h ⁻¹)	0.0149	3.20	35.7	3.61	18.1	0.0150 (3.40)
Fraction of K _{rel} at Cycle >1 (FPC1)	0.762	1.37	25.6	3.37	19.0	0.799 (1.43)
Exponent of Cycle effect on K _{rel} (FPC2)	-0.140	4.51	-	-	-	-0.143 (4.51)
Ritonavir on CL _{DXd}	-0.118	14.9	-	-	-	-0.116 (14.9)
Itraconazole on CL _{DXd}	-0.104	21.9	-	-	-	-0.105 (21.1)
AST (U/L) on CL _{DXd}	-0.230	10.1	-	-	-	-0.230 (11.1)
Total bilirubin (μmol/L) on CL _{DXd}	-0.136	18.4	-	-	-	-0.174 (16.7)
Body weight (kg) on CL _{DXd}	0.438	13.6	-	-	-	0.465 (14.4)
GC on CL _{DXd}	-0.153	17.4	-	-	-	-0.157 (18.0)
NSCLC on CL _{DXd}	-0.210	17.4	-	-	-	-
Other cancer (not BC, GC or NSCLC) on CL _{DXd}	-0.149	35.6	-	-	-	-0.133 (38.1)
Age (yr) on V _{DXd}	0.487	14.8	-	-	-	0.503 (15.9)
FL-DP2 formulation on V _{DXd}	0.314	18.6	-	-	-	0.309 (19.9)
FL-DP1 formulation on V _{DXd}	-0.169	20.3	-	-	-	-0.171 (21.5)
NSCLC on V _{DXd}	-0.392	8.60	-	-	-	-
Other cancer (not BC, GC or NSCLC) on V _{DXd}	-0.202	36.0	-	-	-	-0.245 (24.4)
Race-Country (Non-Asian) on V _{DXd}	-0.207	13.2				-0.177 (17.4)
Residual unexplained variability						
Proportional residual error SD	0.308	0.430	-	-	-	0.302 (0.435)

Notes: RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are calculated as 100×(SE/variance estimate)/2. CV% for the between-subject variability estimates are based on the estimated variances. Shrinkage (%) is calculated as 100 × (1-SD(ETA)/sqrt(variance). Overall residual unexplained variability shrinkage was estimated to be 6.99%.

Source: Population PK report.

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Applicant - Figure 10: Goodness-of-fit Plots for the Final Population PK Model (T-DXd)

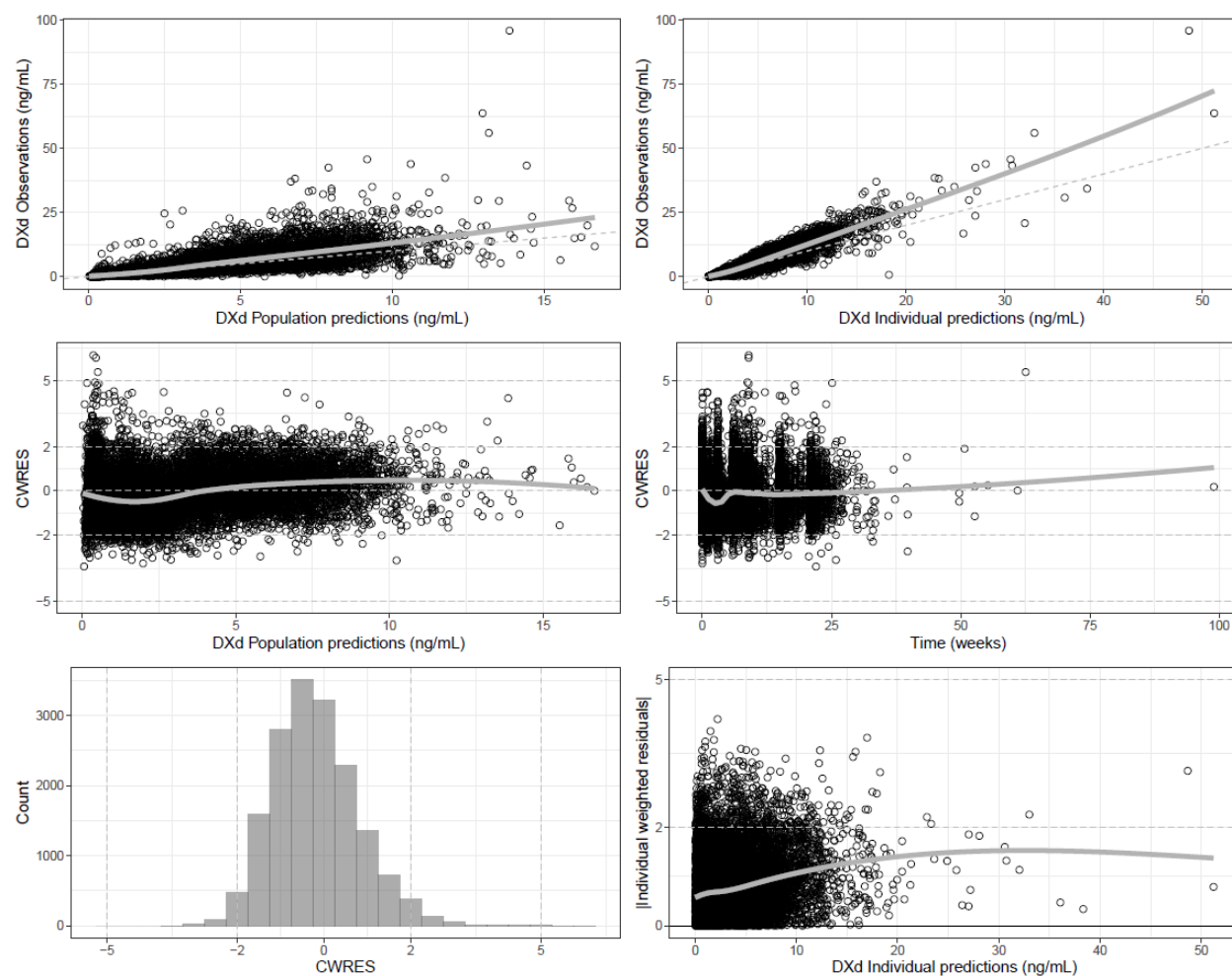


Note: The circles represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.

Source: Population PK report.

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Applicant - Figure 11: Goodness-of-fit Plots for the Final Population PK Model (DXd)

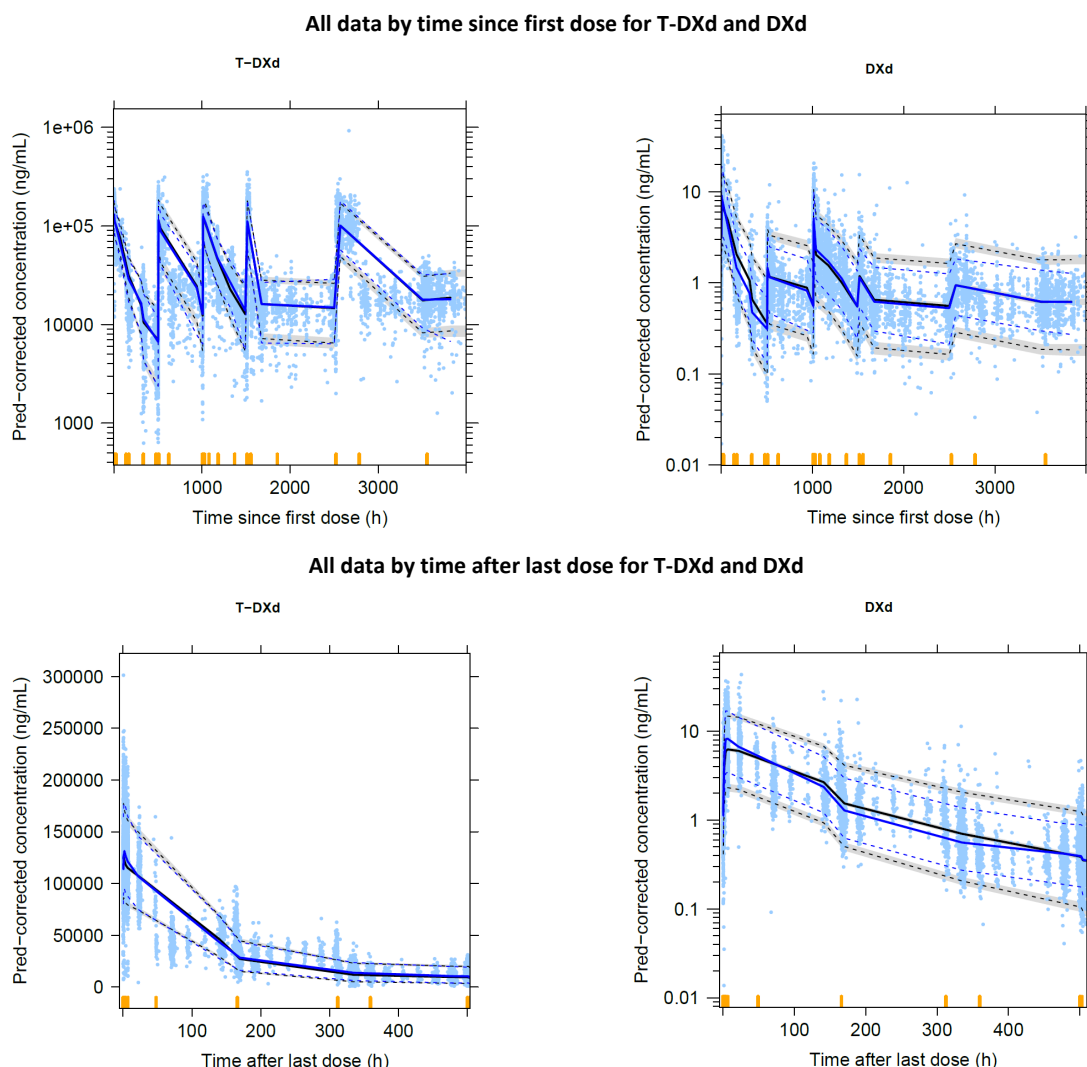


Note: The dots represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.

Source: Population PK report.

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Applicant - Figure 12: Prediction-corrected VPC of Final Population PK Model (T-DXd and DXd), Stratified by Dose



Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals. For DXd, the pred-corrected concentration vs TALD profile (right bottom column) was distorted by the cycle-dependency in the DXd model, hence present an apparent bias. The pred-corrected concentration vs TSFD plot (right top column) suggests reasonable performance of the DXd model.

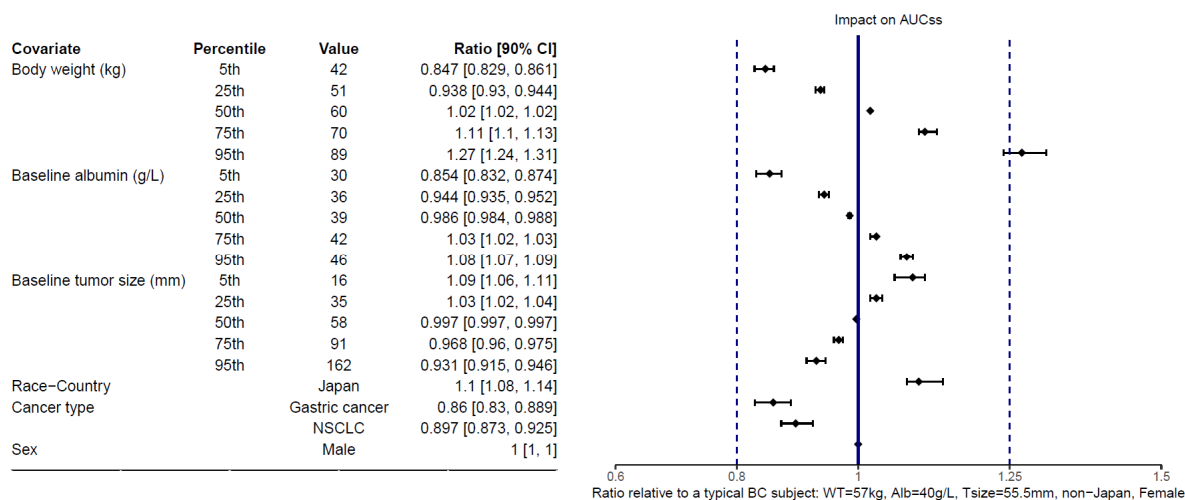
Source: Population PK report.

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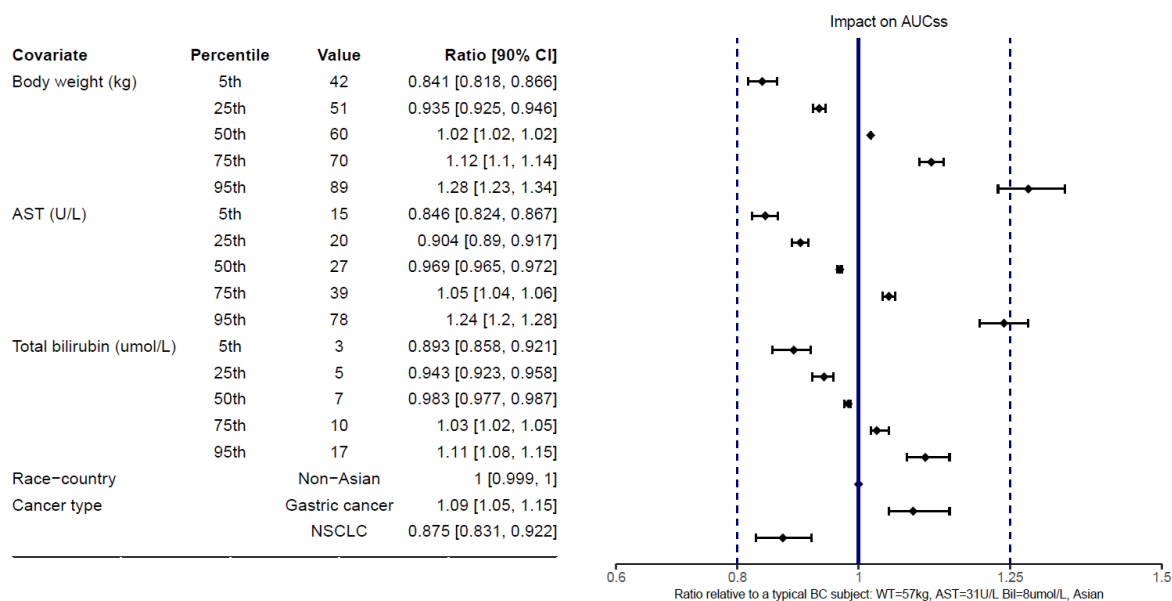
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Applicant - Figure 13: Impact of Significant Covariates on Exposure (T-DXd)



Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the median and 90% CI, respectively. A typical subject is defined as a female subject with BC who is not from Japan with a median weight of 57 kg, albumin of 40 g/L and tumor size of 55.5 mm. Source: Population PK report.

Applicant - Figure 14: Impact of Significant Covariates on Exposure (DXd)



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Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimate and 90% CI, respectively. A typical subject is defined as an Asian subject with BC and a median weight of 57 kg, AST of 31 U/L and total bilirubin of 8 µmol/L. Source: Population PK report.

The FDA's Assessment:

In general, the applicant's population PK analysis is considered acceptable.

PPK Review Issues

In support of proposed dosing regimen for 5.4 mg/kg Q3W of Trastuzumab deruxtecan (T-DXd) in patients with HER-2 mutant NSCLC, the applicant submitted topline results for updated population pharmacokinetic (PPK) report in the briefing documents. The population PK analysis updated from the previous PK model of T-DXd by including the data from Study U206 (from interim analysis with data cut off date 24 Mar 2022) in addition to the previous PK datasets (see section *PPK Assessment Summary*). Summary statistics of the continuous and categorical covariates that were evaluated in the updated PPK analysis are shown in FDA - Table 37 and FDA - Table 38. The final popPK model for T-DXd and DXd was well validated with goodness-of-fit (GOF) plots in the FDA - Figure 15 and FDA - Figure 16. And prediction-corrected visual predictive check (pcVPC) for T-DXd and DXd was shown in the FDA - Figure 17. The final Pop PK model parameters for T-DXd and DXd was shown in the FDA - Table 39 and FDA - Table 40. The updated PPK model is generally in line with previous model (Applicant - Table , Applicant - Table , Applicant - Figure 10, Applicant - Figure 11, Applicant - Figure 12). The potential impact of covariates of interest on the PK of the T-DXd and DXd was assessed. The model parameter estimates for both T-DXd and DXd PK models were consistent with those reported in previous analyses. The covariate effects of interest were evaluated for clinical relevance using forest plots. The covariate analyses showed there were no clinically significant differences in the PK of T-DXd (FDA - Figure 18) and DXd (FDA - Figure 19). The individual exposures such as C_{max}, C_{min} and AUC at cycle 1 and steady state (cycle 9), for both the T-DXd and DXd were generated using the updated model and post hoc PK parameters. The post hoc exposures were comparable among subjects with BC, HER2-mutant NSCLC and HER2-overexpressing NSCLC at 5.4 and 6.4 mg/kg Q3W dose of T-DXd. The addition of data from Study U206 did not change the overall conclusions of the population PK analysis for subjects with NSCLC.

In general, the applicant's updated population PK analysis for T-DXd and DXd is considered acceptable for the purpose of supporting analyses objectives.

FDA - Table 37. Updated Summary of Baseline Continuous Covariates for Study U206

Enhertu® (fam-trastuzumab deruxtecan-nxki)

Variable	n	Mean	Median	SD	Min / Max
Trial: U206					
Baseline age (years)	147	58.8	60.0	11.8	27.0 / 85.0
Body weight at baseline (kg)	147	63.4	61.0	14.7	40.0 / 111
Body surface area at baseline (m^2)	147	1.68	1.65	0.207	1.22 / 2.19
Serum albumin (ALB) at baseline (g/L)	147	38.7	39.0	5.11	23.0 / 52.0
Baseline lactate dehydrogenase (U/L)	147	380	262	359	127 / 2.17e+03
Baseline alanine aminotransferase (U/L)	147	21.8	17.1	16.6	4.04 / 110
Baseline aspartate aminotransferase (U/L)	147	29.9	25.2	16.2	12.0 / 104
Baseline total bilirubin ($\mu\text{mol/L}$)	147	9.13	8.21	4.82	3.00 / 30.8
Baseline creatinine clearance (mL/min)	147	82.3	79.4	26.6	30.2 / 192
Baseline target tumor size (mm)	147	70.4	61.0	43.5	10.0 / 192

Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Table 3.

FDA - Table 38. Updated Summary of Baseline Categorical Covariates by Study

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-XXX)

Enhertu® (fam-trastuzumab deruxtecan-nxki)

	Trial											Summary
	J101	J102	A103	A104	U201	J202	U204	U205	U302	U303	U206	
Formulation												
FL-DP1	265 (92.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	265 (14.5)
FL-DP2	21 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	142 (56.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	163 (8.9)
Lyo-DP	0 (0.0)	51 (100.0)	12 (100.0)	40 (100.0)	108 (43.2)	169 (100.0)	175 (100.0)	76 (100.0)	254 (100.0)	362 (100.0)	147 (100.0)	1394 (76.5)
Sex of the subject												
male	62 (21.7)	0 (0.0)	0 (0.0)	18 (45.0)	0 (0.0)	128 (75.7)	81 (46.3)	55 (72.4)	1 (0.4)	2 (0.6)	50 (34.0)	397 (21.8)
female	224 (78.3)	51 (100.0)	12 (100.0)	22 (55.0)	250 (100.0)	41 (24.3)	94 (53.7)	21 (27.6)	253 (99.6)	360 (99.4)	97 (66.0)	1425 (78.2)
Race												
White	80 (28.0)	0 (0.0)	0 (0.0)	0 (0.0)	132 (52.8)	0 (0.0)	100 (57.1)	67 (88.2)	70 (27.6)	170 (47.0)	27 (18.4)	646 (35.5)
Black or African American	8 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)	7 (4.0)	1 (1.3)	9 (3.5)	6 (1.7)	2 (1.4)	38 (2.1)
Asian	190 (66.4)	51 (100.0)	12 (100.0)	40 (100.0)	101 (40.4)	169 (100.0)	45 (25.7)	3 (3.9)	148 (58.3)	147 (40.6)	92 (62.6)	998 (54.8)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)	0 (0.0)	4 (0.2)
Other	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.4)	0 (0.0)	22 (12.6)	3 (3.9)	27 (10.6)	38 (10.5)	26 (17.7)	129 (7.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.3)
Country												
Japan	177 (61.9)	51 (100.0)	0 (0.0)	31 (77.5)	53 (21.2)	134 (79.3)	36 (20.6)	0 (0.0)	36 (14.2)	53 (14.6)	52 (35.4)	623 (34.2)
Korea	0 (0.0)	0 (0.0)	0 (0.0)	7 (17.5)	40 (16.0)	35 (20.7)	0 (0.0)	0 (0.0)	36 (14.2)	38 (10.5)	27 (18.4)	183 (10.0)
Taiwan	0 (0.0)	0 (0.0)	12 (100.0)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (11.8)	8 (2.2)	11 (7.5)	63 (3.5)
United States of America	109 (38.1)	0 (0.0)	0 (0.0)	0 (0.0)	77 (30.8)	0 (0.0)	65 (37.1)	33 (43.4)	15 (5.9)	53 (14.6)	4 (2.7)	356 (19.5)
Belgium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.6)	0 (0.0)	0 (0.0)	3 (3.9)	2 (0.8)	11 (3.0)	0 (0.0)	25 (1.4)
Spain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (11.6)	0 (0.0)	27 (15.4)	4 (5.3)	8 (3.1)	34 (9.4)	6 (4.1)	108 (5.9)
Italy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.0)	0 (0.0)	0 (0.0)	20 (26.3)	14 (5.5)	19 (5.2)	9 (6.1)	72 (4.0)
Great Britain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (4.8)	0 (0.0)	0 (0.0)	16 (21.1)	8 (3.1)	6 (1.7)	0 (0.0)	42 (2.3)
France	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (8.0)	0 (0.0)	17 (9.7)	0 (0.0)	20 (7.9)	39 (10.8)	26 (17.7)	122 (6.7)
China	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	35 (13.8)	44 (12.2)	0 (0.0)	79 (4.3)
Hong Kong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.5)	0 (0.0)	0 (0.0)	9 (0.5)
Netherlands	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (5.4)	38 (2.1)
Canada	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	3 (0.8)	1 (0.7)	6 (0.3)
Brasil	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (12.6)	0 (0.0)	0 (0.0)	32 (1.8)
Australia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.8)	0 (0.0)	3 (2.0)	10 (0.5)
Greece	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.5)	0 (0.0)	9 (0.5)
Portugal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.8)	0 (0.0)	10 (0.5)
Hungary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.2)
Switzerland	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.5)	0 (0.0)	9 (0.5)
Austria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)	0 (0.0)	4 (0.2)
Sweden	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)	0 (0.0)	4 (0.2)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-XXX)

Enhertu® (fam-trastuzumab deruxtecan-nxki)

	Trial											Summary
	J101	J102	A103	A104	U201	J202	U204	U205	U302	U303	U206	
Russia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)	0 (0.0)	4 (0.2)
Israel	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (3.0)	0 (0.0)	11 (0.6)
Japan race-country												
Asian from Japan	177 (61.9)	51 (100.0)	0 (0.0)	31 (77.5)	53 (21.2)	134 (79.3)	36 (20.6)	0 (0.0)	36 (14.2)	53 (14.6)	52 (35.4)	623 (34.2)
Asian not from Japan	14 (4.9)	0 (0.0)	12 (100.0)	9 (22.5)	49 (19.6)	35 (20.7)	9 (5.1)	3 (3.9)	112 (44.1)	94 (26.0)	40 (27.2)	377 (20.7)
Non-Asian	95 (33.2)	0 (0.0)	0 (0.0)	0 (0.0)	148 (59.2)	0 (0.0)	130 (74.3)	73 (96.1)	106 (41.7)	215 (59.4)	55 (37.4)	822 (45.1)
China race-country												
Mainland China	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	35 (13.8)	44 (12.2)	0 (0.0)	79 (4.3)
Hong Kong and Taiwan	0 (0.0)	0 (0.0)	12 (100.0)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	39 (15.4)	8 (2.2)	11 (7.5)	72 (4.0)
Rest of World	286 (100.0)	51 (100.0)	0 (0.0)	38 (95.0)	250 (100.0)	169 (100.0)	175 (100.0)	76 (100.0)	180 (70.9)	310 (85.6)	136 (92.5)	1671 (91.7)
Population type												
Breast	182 (63.6)	51 (100.0)	12 (100.0)	17 (42.5)	250 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	254 (100.0)	362 (100.0)	0 (0.0)	1128 (61.9)
Gastric/Gastro-esophageal junction	47 (16.4)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	169 (100.0)	0 (0.0)	76 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	293 (16.1)
CRC	20 (7.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (1.2)
NSCLC	18 (6.3)	0 (0.0)	0 (0.0)	6 (15.0)	0 (0.0)	0 (0.0)	175 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	147 (100.0)	346 (19.0)
Other	19 (6.6)	0 (0.0)	0 (0.0)	15 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	34 (1.9)
ECOG performance status												
0	177 (61.9)	31 (60.8)	3 (25.0)	21 (52.5)	143 (57.2)	83 (49.1)	41 (23.4)	27 (35.5)	151 (59.4)	194 (53.6)	47 (32.0)	918 (50.4)
1	109 (38.1)	20 (39.2)	9 (75.0)	19 (47.5)	106 (42.4)	86 (50.9)	134 (76.6)	49 (64.5)	103 (40.6)	168 (46.4)	100 (68.0)	903 (49.6)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Baseline hepatic impairment												
normal	169 (59.1)	28 (54.9)	9 (75.0)	30 (75.0)	141 (56.4)	114 (67.5)	159 (90.9)	64 (84.2)	205 (80.7)	165 (45.6)	114 (77.6)	1198 (65.8)
mild	117 (40.9)	23 (45.1)	3 (25.0)	10 (25.0)	104 (41.6)	53 (31.4)	15 (8.6)	11 (14.5)	49 (19.3)	190 (52.5)	33 (22.4)	608 (33.4)
moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	6 (0.3)
severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	1 (0.6)	1 (1.3)	0 (0.0)	5 (1.4)	0 (0.0)	10 (0.5)
Antidrug antibodies flag												
negative subject ADA status	281 (98.3)	48 (94.1)	12 (100.0)	39 (97.5)	235 (94.0)	145 (85.8)	155 (88.6)	69 (90.8)	236 (92.9)	336 (92.8)	140 (95.2)	1696 (93.1)
positive subject ADA status	5 (1.7)	3 (5.9)	0 (0.0)	1 (2.5)	15 (6.0)	24 (14.2)	20 (11.4)	7 (9.2)	18 (7.1)	26 (7.2)	7 (4.8)	126 (6.9)
Baseline HER2 status												
Negative	14 (4.9)	0 (0.0)	0 (0.0)	2 (5.0)	1 (0.4)	44 (26.0)	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)	65 (3.6)
Positive	184 (64.3)	4 (7.8)	12 (100.0)	23 (57.5)	249 (99.6)	123 (72.8)	0 (0.0)	75 (98.7)	249 (98.0)	0 (0.0)	0 (0.0)	919 (50.4)
Mutant	11 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	88 (50.3)	0 (0.0)	0 (0.0)	0 (0.0)	147 (100.0)	246 (13.5)
Overexpressing	7 (2.4)	0 (0.0)	0 (0.0)	6 (15.0)	0 (0.0)	0 (0.0)	87 (49.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	100 (5.5)
Low	53 (18.5)	47 (92.2)	0 (0.0)	6 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	362 (100.0)	0 (0.0)	468 (25.7)
Missing	17 (5.9)	0 (0.0)	0 (0.0)	3 (7.5)	0 (0.0)	2 (1.2)	0 (0.0)	1 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)	24 (1.3)
Renal impairment												
Normal renal function	125 (43.7)	23 (45.1)	5 (41.7)	19 (47.5)	121 (48.4)	48 (28.4)	60 (34.3)	36 (47.4)	134 (52.8)	199 (55.0)	0 (0.0)	770 (42.3)
Mild impairment	119 (41.6)	23 (45.1)	7 (58.3)	17 (42.5)	96 (38.4)	72 (42.6)	73 (41.7)	28 (36.8)	94 (37.0)	117 (32.3)	66 (44.9)	712 (39.1)

Enhertu® (fam-trastuzumab deruxtecan-nxki)

	Trial											Summary
	J101	J102	A103	A104	U201	J202	U204	U205	U302	U303	U206	
Moderate impairment	41 (14.3)	5 (9.8)	0 (0.0)	4 (10.0)	33 (13.2)	49 (29.0)	40 (22.9)	12 (15.8)	26 (10.2)	41 (11.3)	28 (19.0)	279 (15.3)
Severe impairment	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	4 (0.2)
Kidney failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	53 (36.1)	53 (2.9)
NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)	0 (0.0)	4 (0.2)

Source: Applicant's Brief Communication titled *Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors*, Table 4.

FDA - Table 39. Updated Parameter Estimates and Standard Error from Final Population PK Model (T-DXd)

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Enhertu® (fam-trastuzumab deruxtecan-nxki)

			Estimate	95% CI
Structural model parameters				
CL (L/day)	θ_1	T-DXd clearance	0.409	0.402, 0.417
V1 (L)	θ_2	T-DXd central volume	2.69	2.66, 2.72
Q (L/day)	θ_3	T-DXd inter-compartmental clearance	0.195	0.190, 0.199
V2 (L)	θ_4	T-DXd peripheral volume	6.46	6.08, 6.84
Covariate effect parameters				
CL ~ ALB	θ_7	Baseline serum albumin effect on CL	-0.472	-0.565, -0.380
CL ~ JPGR1	θ_8	If Asian from Japan effect on CL	-0.0855	-0.111, -0.0604
CL ~ TTUMB	θ_{10}	Baseline target tumor size effect on CL	0.0506	0.0341, 0.0670
CL ~ WGTB	θ_{11}	Baseline body weight effect on CL	0.399	0.338, 0.461
CL ~ GC	θ_{15}	If GC effect on CL	0.168	0.124, 0.213
CL ~ NSCLC HER2 mutant	θ_{16}	If NSCLC with HER2 mutant effect on CL	0.0155	-0.0222, 0.0532
CL ~ NSCLC HER2 overexpressing	θ_{17}	If NSCLC with HER2 overexpressing effect on CL	0.140	0.0750, 0.204
CL ~ CRC or others	θ_{18}	If cancer types other than BC, GC or NSCLC effect on CL	0.0708	-0.00916, 0.151
V1 ~ SEX	θ_{12}	Sex effect on V1	0.131	0.102, 0.161
V1 ~ WGTB	θ_{13}	Baseline body weight effect on V1	0.443	0.402, 0.484
V1 ~ GC	θ_{19}	If GC effect on V1	0.100	0.0672, 0.133
V1 ~ NSCLC HER2 mutant	θ_{20}	If NSCLC with HER2 mutant effect on V1	-0.0689	-0.0914, -0.0463
V1 ~ NSCLC HER2 overexpressing	θ_{21}	If NSCLC with HER2 overexpressing effect on V1	-0.0185	-0.0636, 0.0265
V2 ~ JPGR1	θ_{14}	If Asian from Japan effect on V2	-0.238	-0.308, -0.168

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		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL	$\Omega_{(1,1)}$	0.0589 [CV%=24.6]	0.0550, 0.0628	10.7
IIV-V1	$\Omega_{(2,2)}$	0.0251 [CV%=15.9]	0.0240, 0.0262	8.40
IIV-Q	$\Omega_{(3,3)}$	0.0815 [CV%=29.1]	0.0682, 0.0948	40.1
IIV-V2	$\Omega_{(4,4)}$	0.503 [CV%=80.9]	0.444, 0.563	24.3
Interindividual covariance parameters				
CL-V1	$\Omega_{(2,1)}$	0.0209 [Corr=0.543]	0.0191, 0.0227	-
Residual variance				
T-DXd proportional	θ_5	0.169	0.169, 0.170	-
T-DXd additive	θ_6	1040	1000, 1070	-

Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Table 5 & 6.

FDA - Table 40. Updated Parameter Estimates and SE from Final Population PK Model (DXd)

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			Estimate	95% CI
Structural model parameters				
CLPAY (L/h)	θ_{23}	DXd clearance	19.6	18.8, 20.4
KREL (/h)	θ_{24}	DXd release rate constant	0.0197	0.0189, 0.0206
FPC1	θ_{27}	DXd deconjugation fraction at CYCLE>1	0.732	0.718, 0.745
FPC2	θ_{28}	DXd deconjugation fraction power cycle effect	-0.155	-0.163, -0.146
V3 (L)	NA	DXd volume	17*BSA	FIXED
Covariate effect parameters				
CLPAY ~ RITONVR	θ_{29}	Ritonavir effect on CLPAY	-0.122	-0.156, -0.0871
CLPAY ~ ITRACNZL	θ_{30}	Itraconazole effect on CLPAY	-0.109	-0.152, -0.0661
CLPAY ~ SGOTB	θ_{31}	Baseline aspartate aminotransferase effect on CLPAY	-0.195	-0.233, -0.157
CLPAY ~ BILITLB	θ_{32}	Baseline total bilirubin effect on CLPAY	-0.139	-0.178, -0.0997
CLPAY ~ WGTB	θ_{33}	Baseline body weight effect on CLPAY	0.341	0.246, 0.437
V3 ~ AGE	θ_{34}	Age effect on V3	0.590	0.471, 0.709
V3 ~ FORM1	θ_{35}	If FL-DP2 effect on V3	0.579	0.443, 0.714
V3 ~ NSCLC	θ_{38}	If NSCLC effect on V3	-0.247	-0.309, -0.185
V3 ~ JPGR3	θ_{44}	If non-Asian effect on V3	-0.236	-0.277, -0.195

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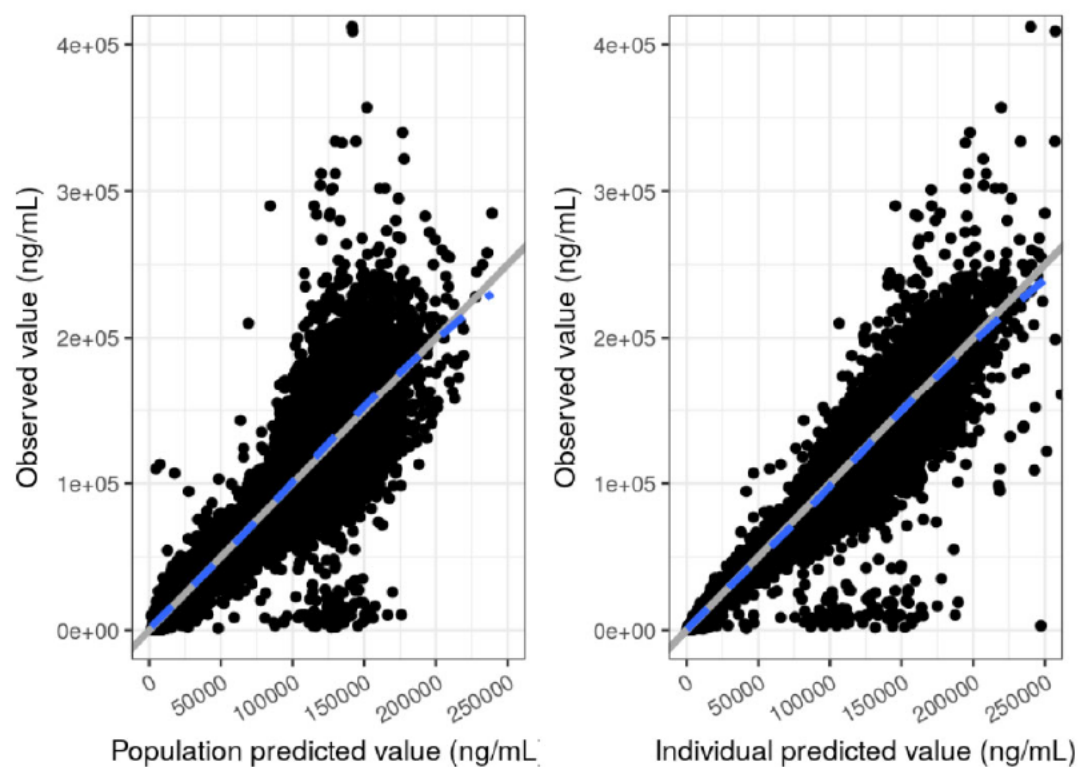
		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CLPAY	$\Omega_{(5,5)}$	0.0852 [CV%=29.8]	0.0734, 0.0969	33.5
IIV-V3	$\Omega_{(6,6)}$	0.193 [CV%=46.1]	0.173, 0.212	22.4
IIV-KREL	$\Omega_{(7,7)}$	0.103 [CV%=33.0]	0.0896, 0.117	25.1
IIV-FPC1	$\Omega_{(8,8)}$	0.666 [SD=0.164]	0.569, 0.762	26.8
Residual variance				
DXd proportional	θ_{25}	0.309	0.307, 0.311	-

Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Table 7&8.

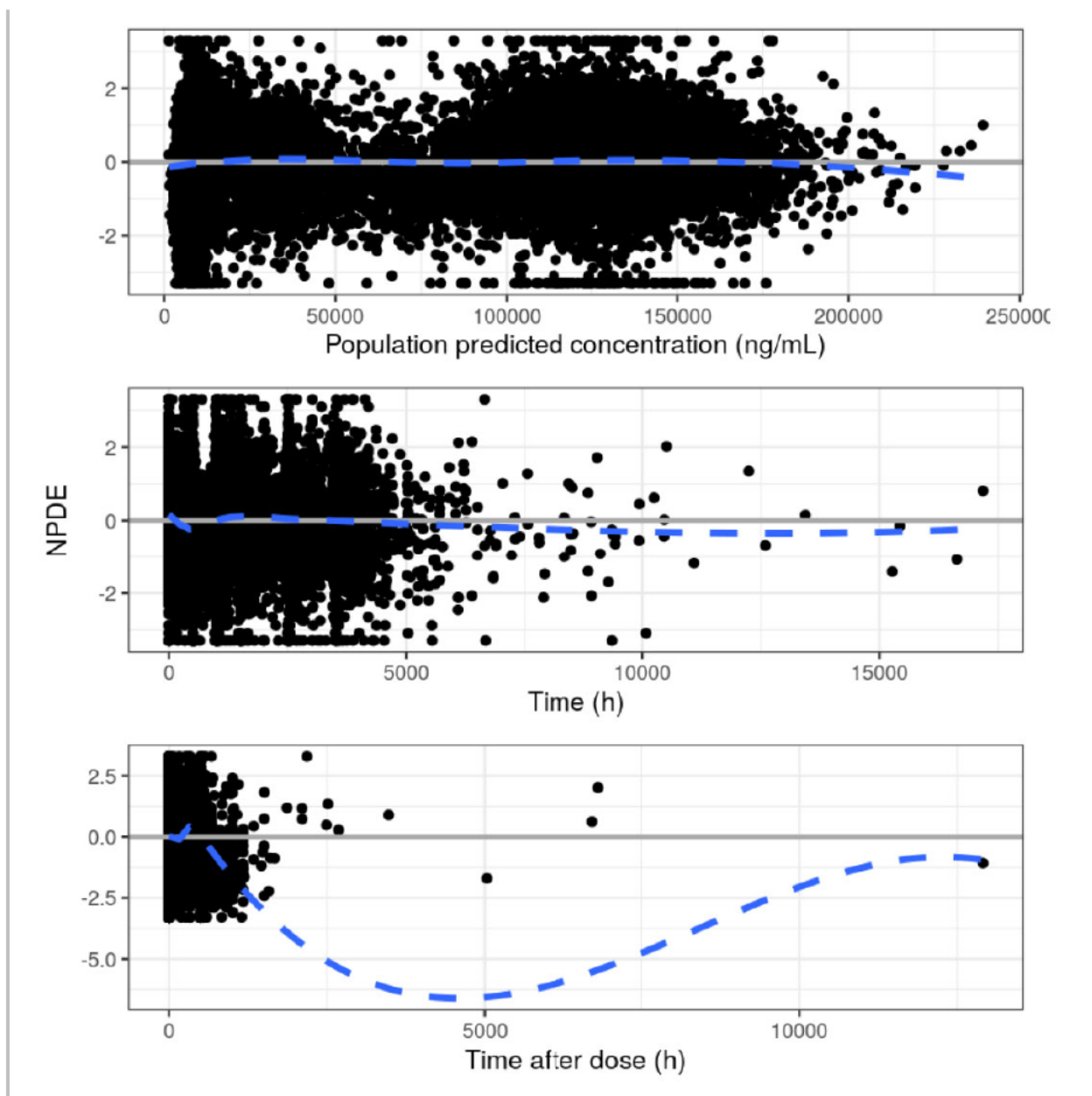
FDA - Figure 15. Updated Goodness-of-fit Plots for the Final Population PK Model (T-DXd)

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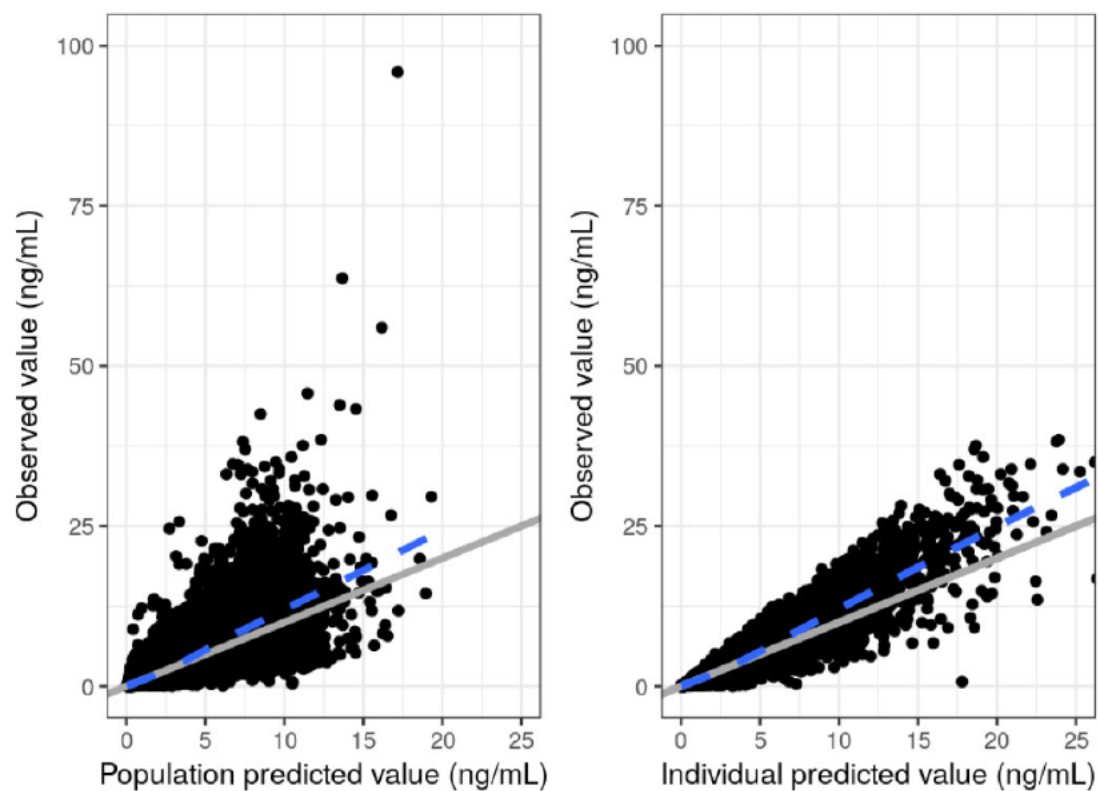


Source: Applicant's Brief Communication titled *Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors*, Figure 1&3.

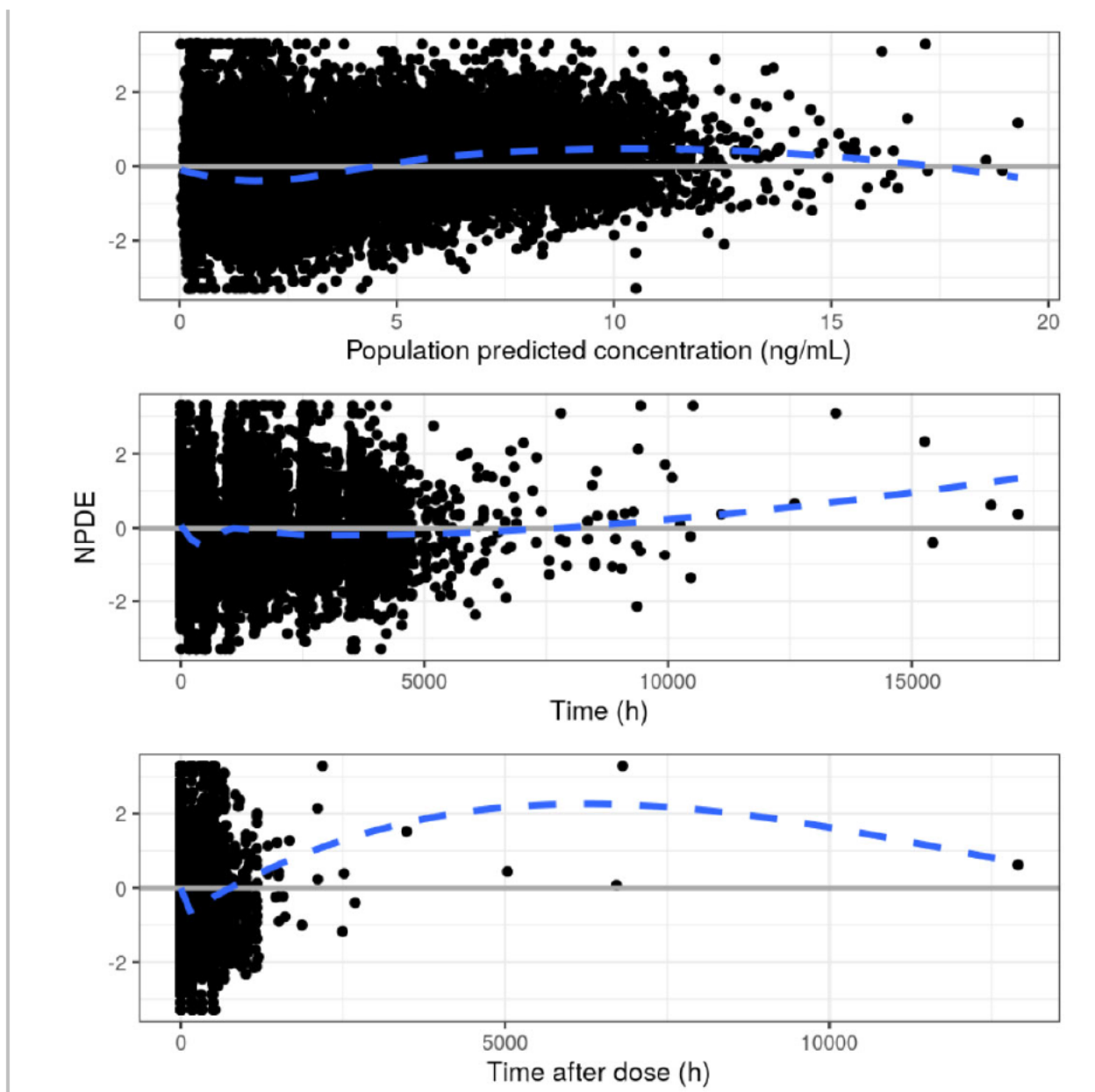
FDA - Figure 16. Updated Goodness-of-fit Plots for the Final Population PK Model (DXd)

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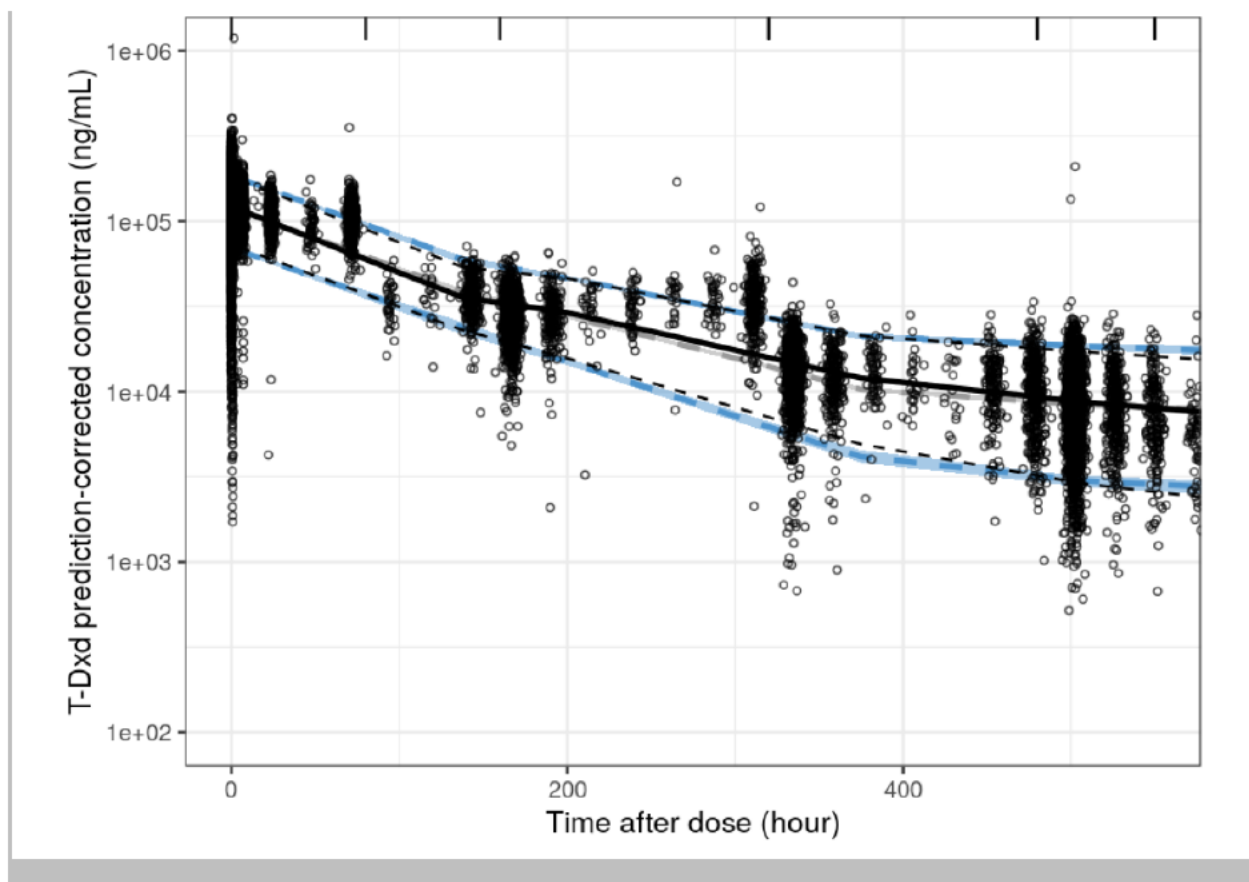


Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Figure 2&4.

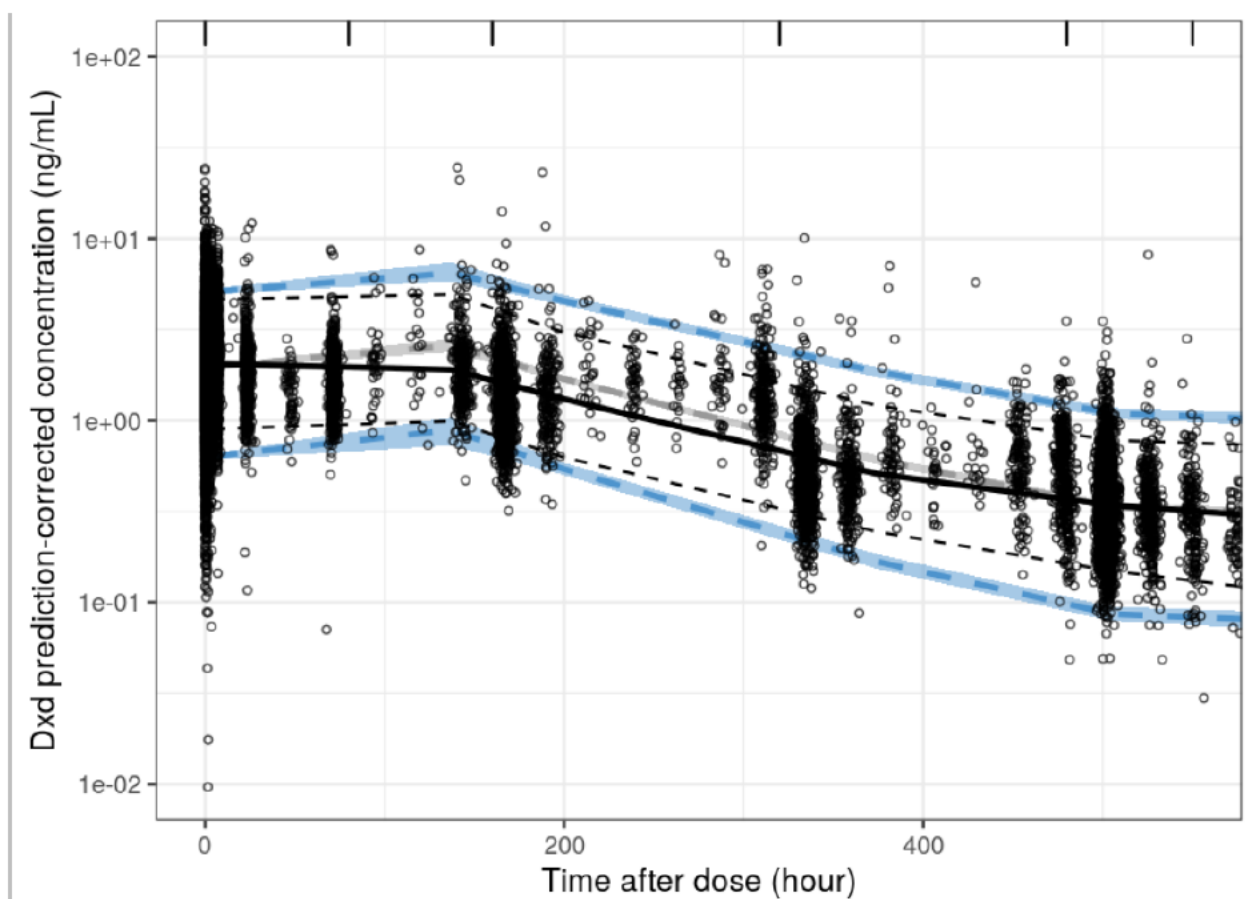
FDA - Figure 17. Updated Prediction-corrected VPC of Final Population PK Model (T-DXd and DXd)

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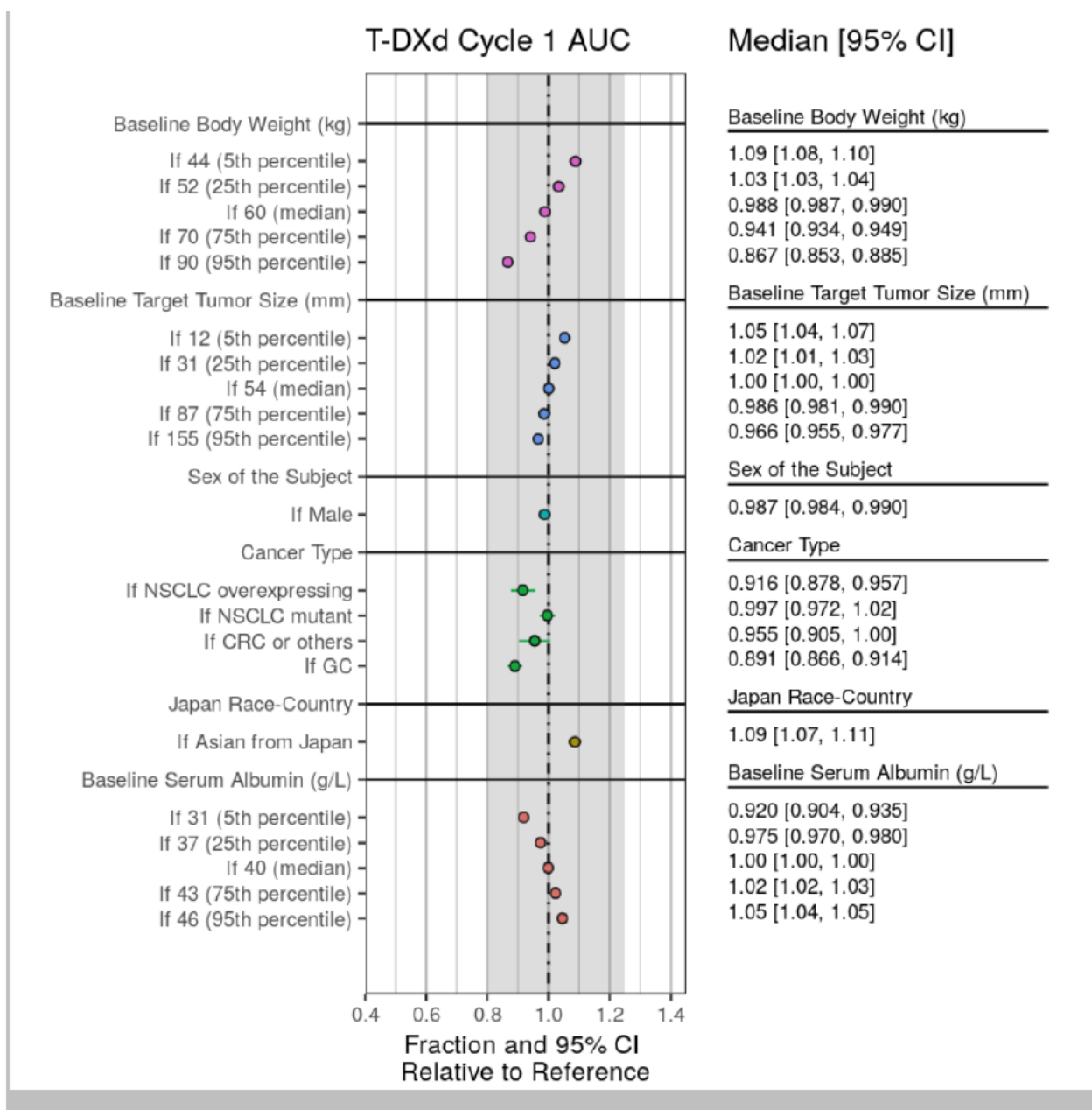
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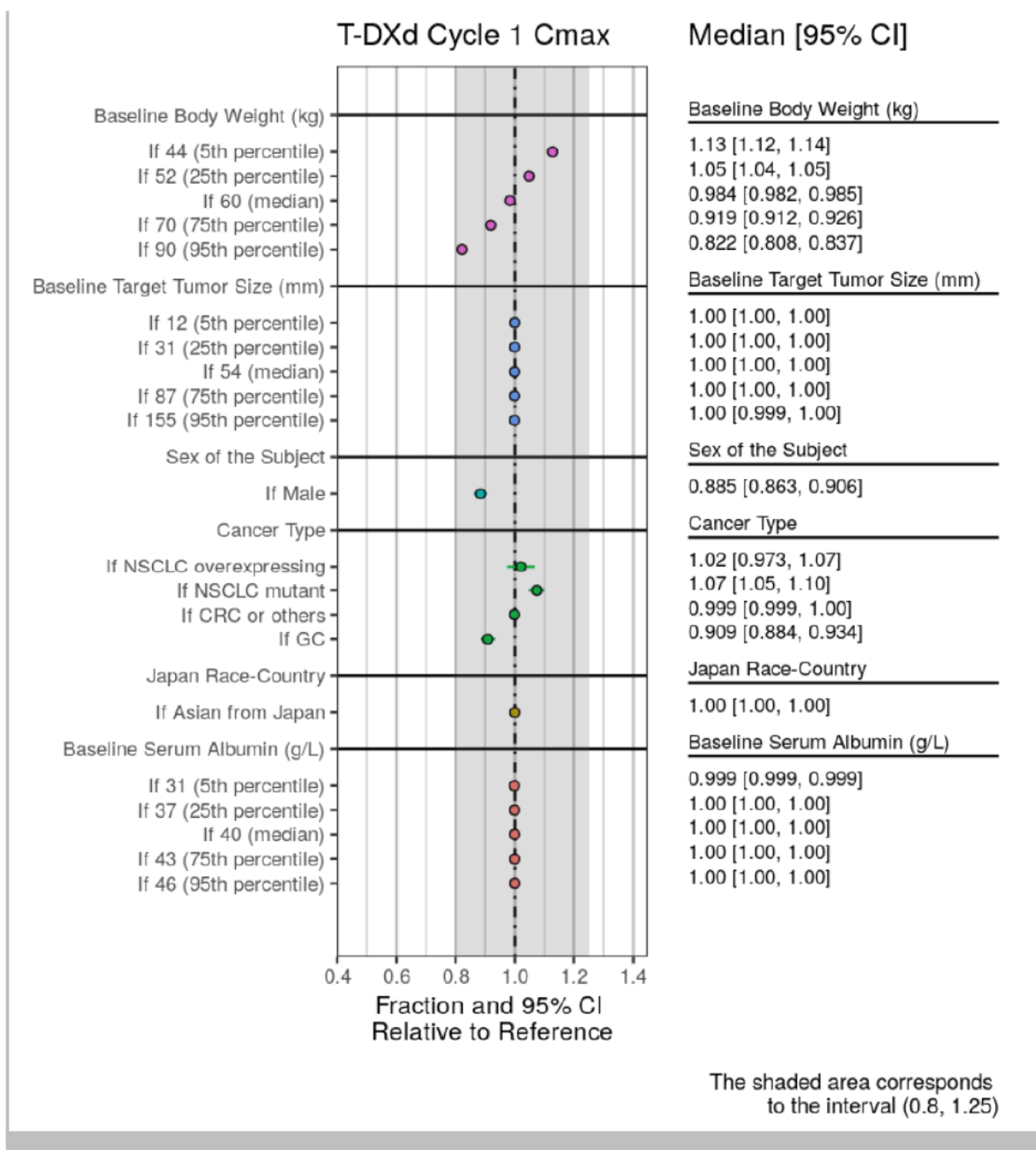
Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Figure 55 & 56.

FDA - Figure 18. Updated Forest Plot for Impact of Significant Covariates on Exposure AUC and Cmax of T-DXd at Cycle 1 and Cycle 9

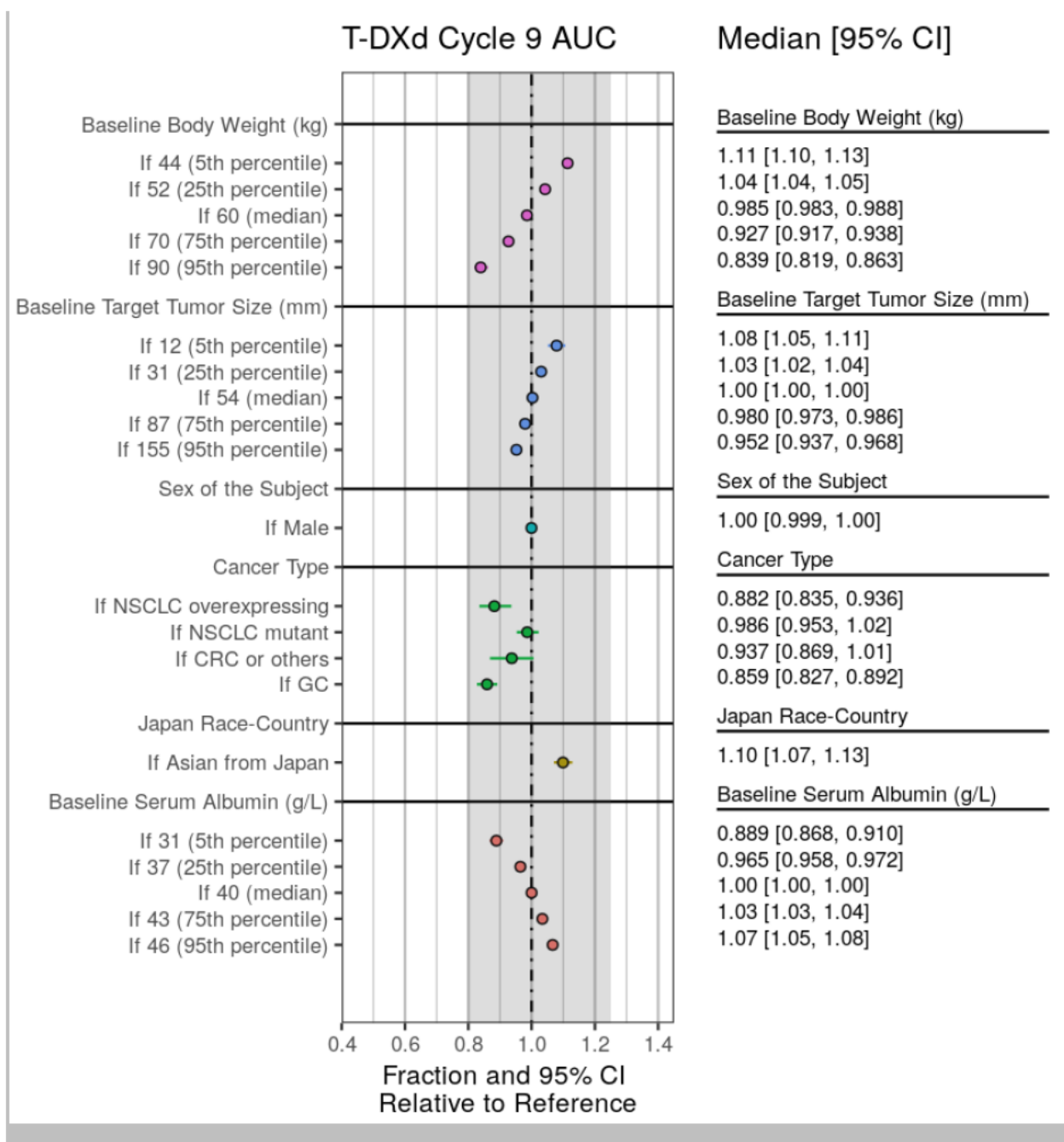
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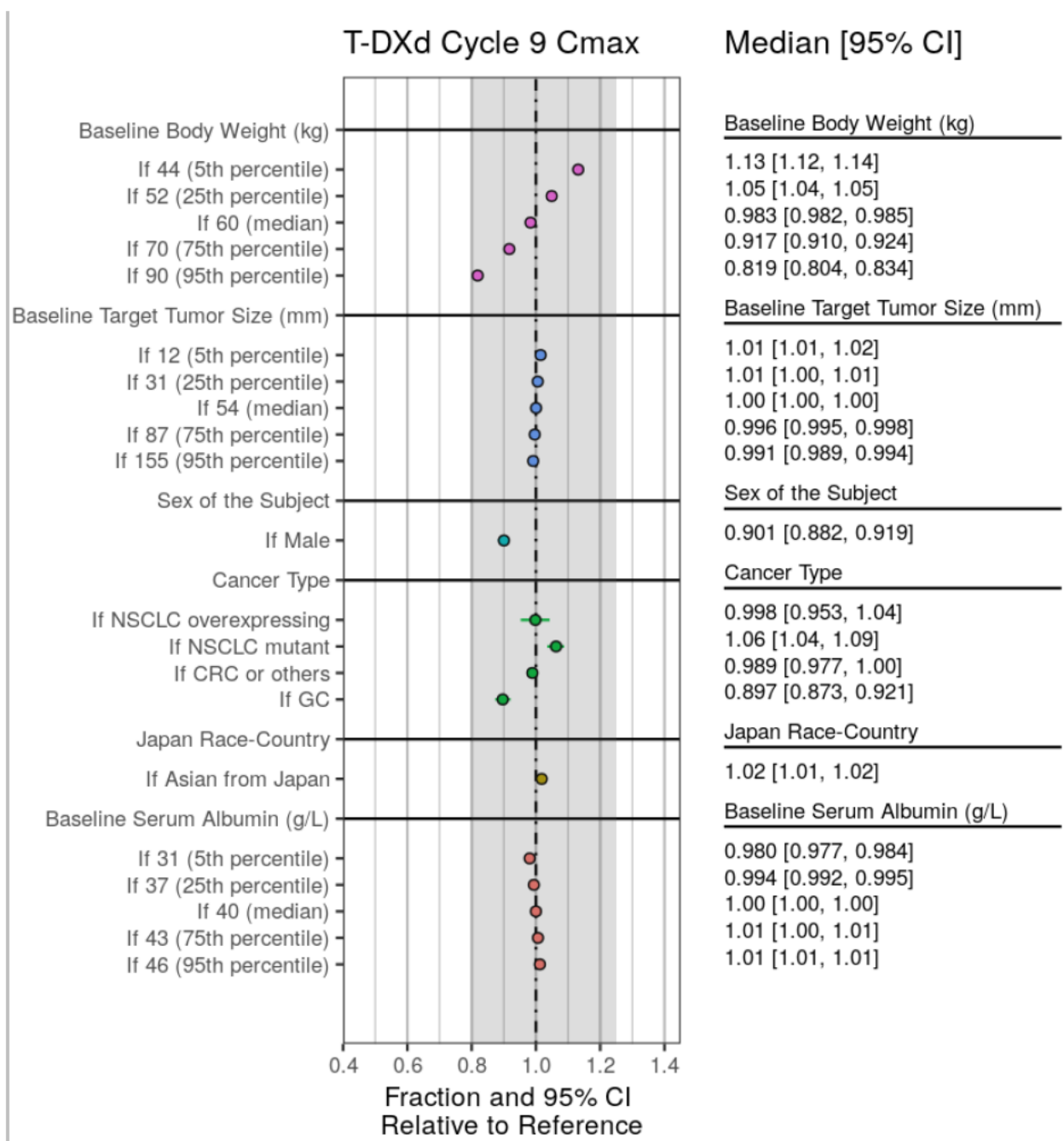
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The reference group is female BC Asian not from Japan subjects with 57.8 kg baseline body weight, 57mm baseline target tumor size and 40 g/L baseline serum albumin

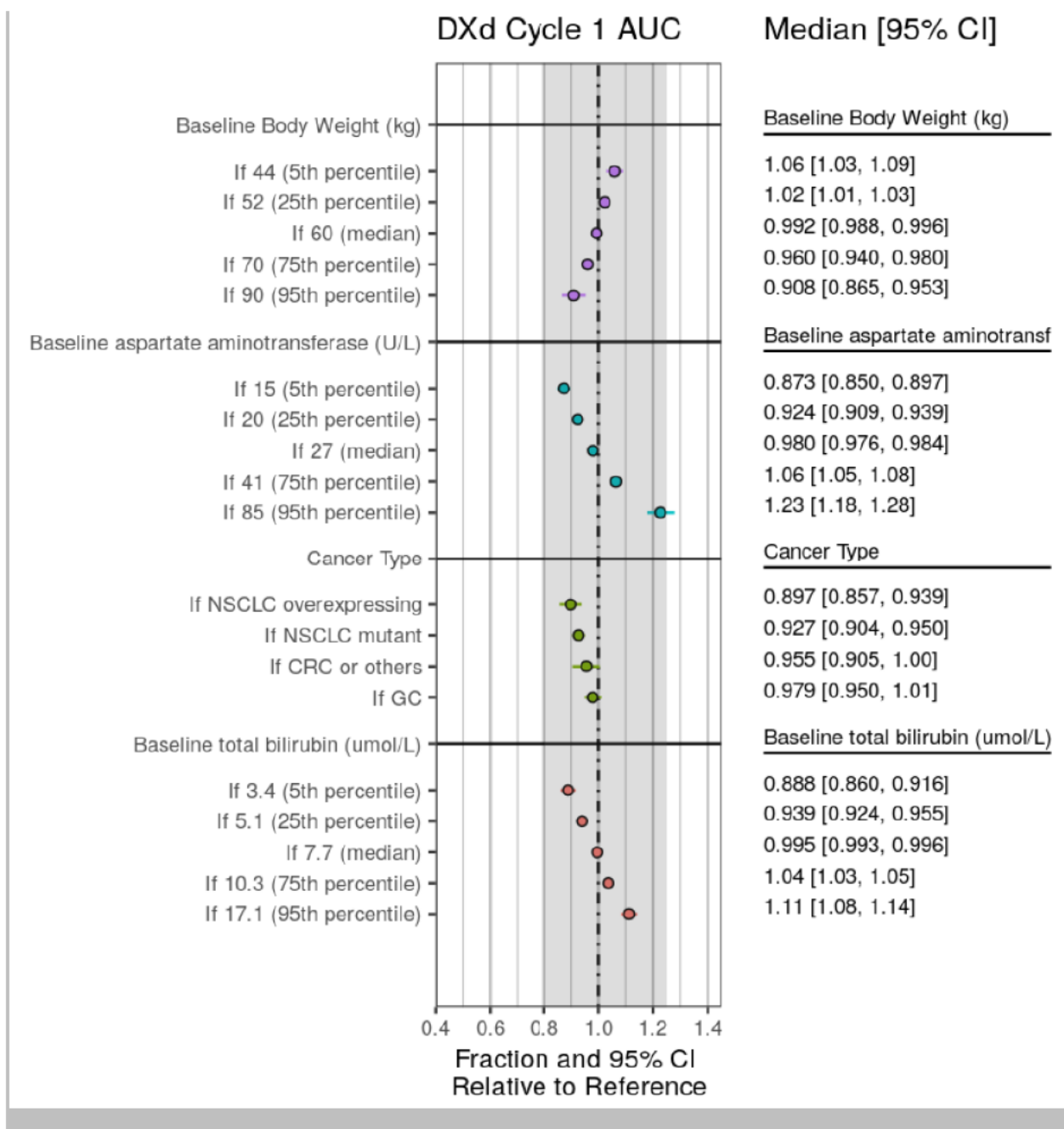
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Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Figure 63, 64, 65 & 66.

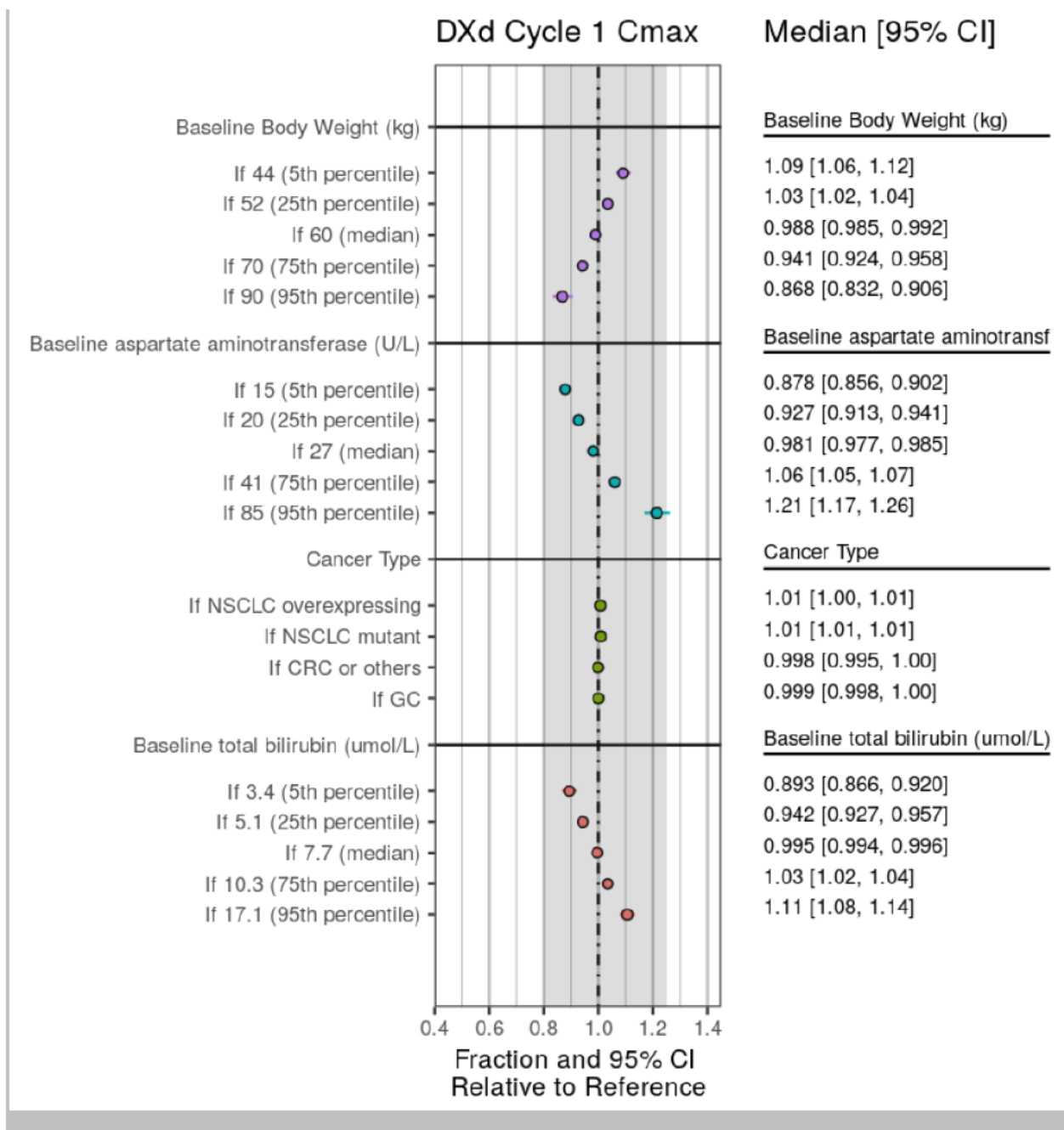
FDA - Figure 19. Updated Forest Plot for Impact of Significant Covariates on Exposure AUC and Cmax of DXd at Cycle 1 and Cycle 9

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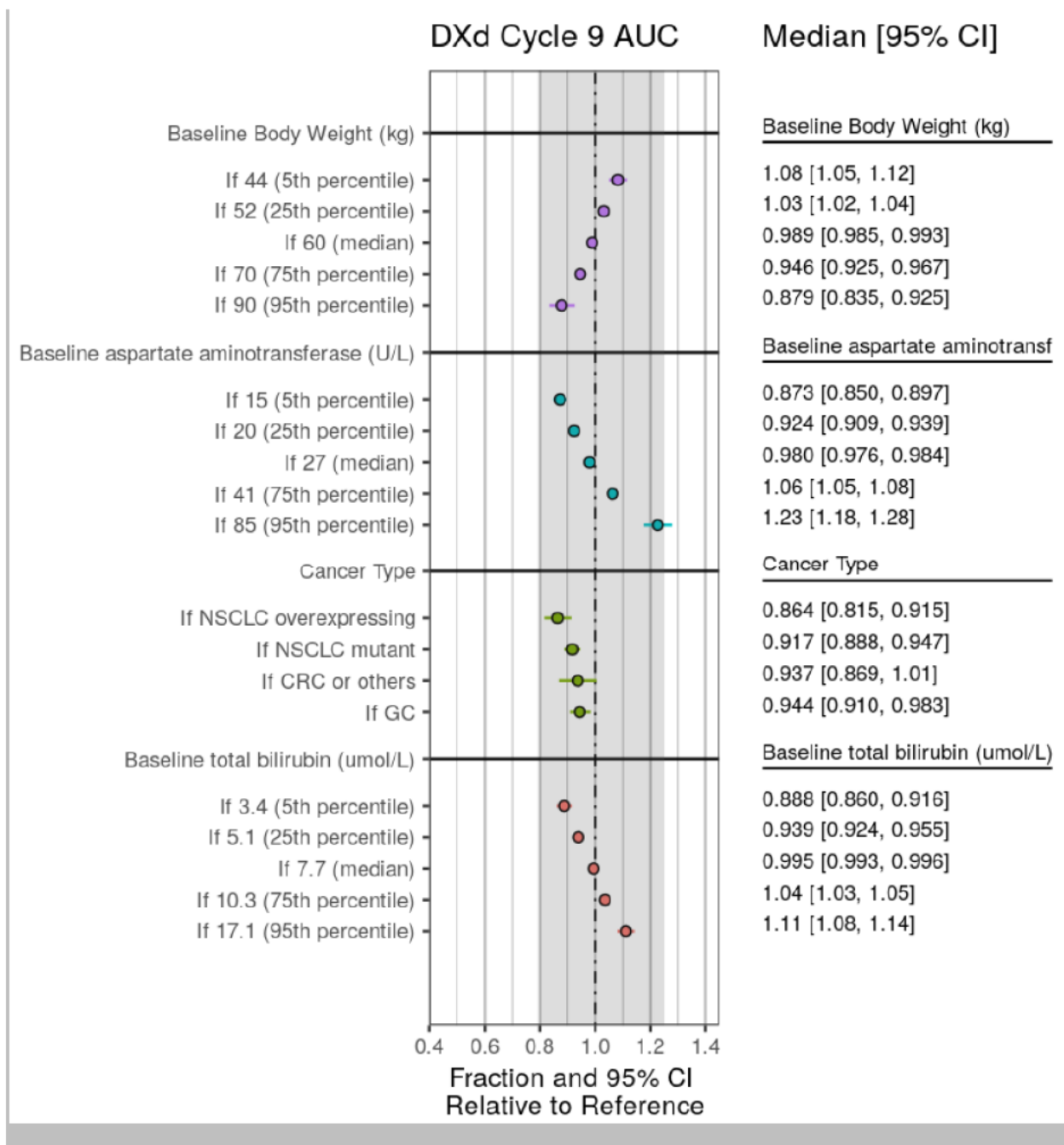
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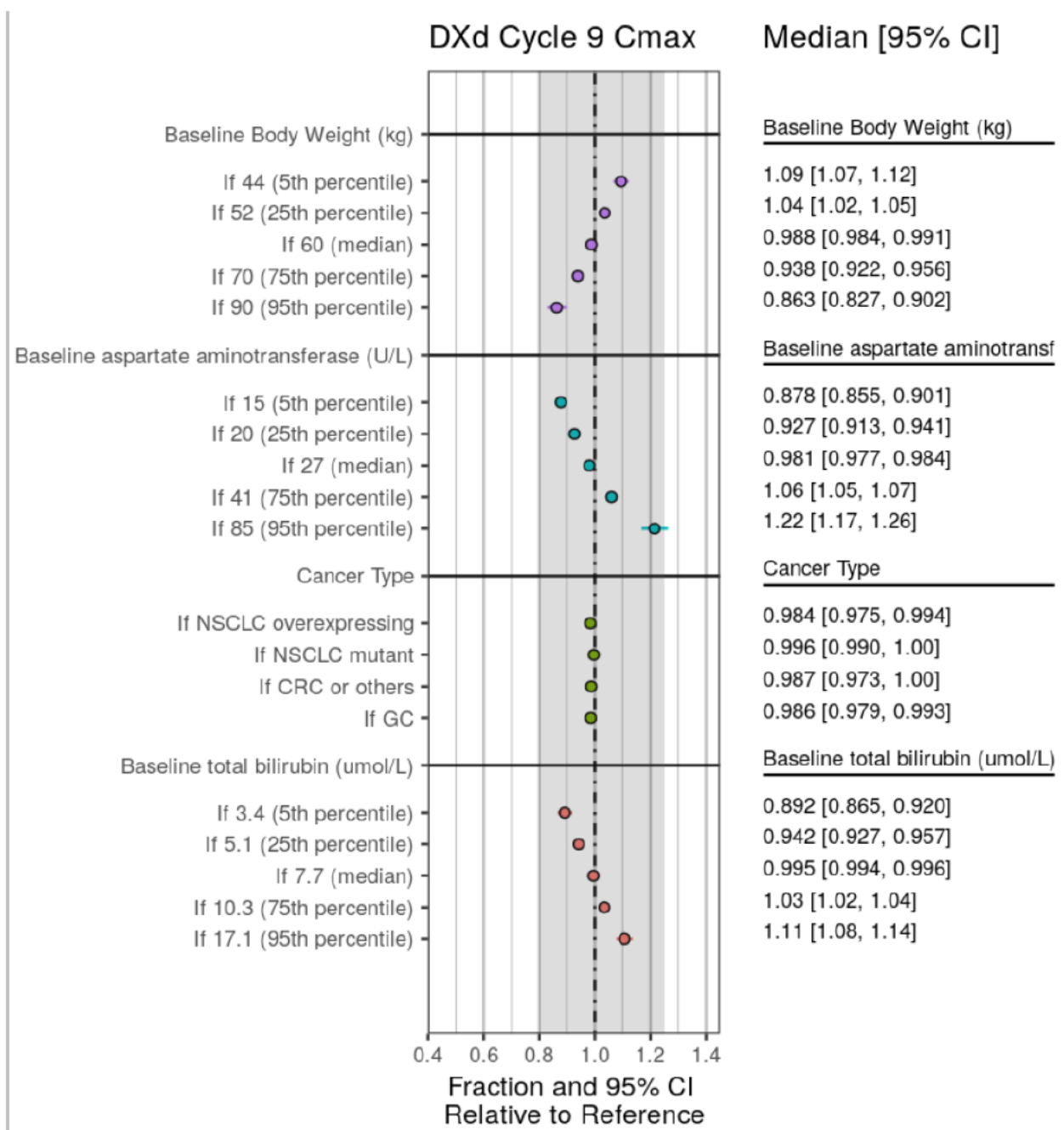


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The reference group is BC subjects with 57.8 kg baseline body weight, 30 U/L baseline aspartate aminotransferase and 8 umol/L baseline total bilirubin.

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Source: Applicant's Brief Communication titled Trastuzumab Deruxtecan Population Pharmacokinetics in Subjects with HER2-mutant and HER2-overexpressing Non-Small Cell Lung Cancer and Other Solid Tumors, Figure 67, 68, 69 & 70.

Reviewer's Independent Analysis

None.

19.4.2 Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

In support of this BLA, the applicant submitted topline reports of exposure-response (E-R) for efficacy analyses. Applicant's Exposure-response analyses for efficacy updated an existing model of ORR in the HER2-mutant NSCLC population with updated efficacy data from Study U204 (DCO date 3 Dec 2021) and newly available efficacy data from Study U206 (DCO date 24 Mar 2022) and prior data from patients with HER2-mutant NSCLC from Study J101. The primary efficacy endpoint for E-R analyses is the ORR. The E-R analysis for efficacy results showed T-DXd exposure had a positive but shallow relationship with ORR. And the updated E-R results are generally consistent with prior ER analyses conducted using data from patients with NSCLC from Studies J101 and U204.

Overall, the applicant's E-R analysis for efficacy appears adequate. The flat E-R relationship for efficacy endpoints may imply that the effectiveness of T-DXd reached a plateau, which supports the proposed dosage of 5.4 mg/kg Q3W.

ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	To develop the ER relationship for ORR, BTR, and longitudinal tumor size (SoD) to support the dosing recommendation of T-DXd in patients with HER2-mutant NSCLC.
Study Included	J101, U201, J202, U204, and U205

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Endpoint		ORR, BTR, longitudinal tumor size measurements, where tumor size was measured as the SoD per RECIST v1.1	
No. of Patients (total, and with individual PK)		765 subjects: 97 subjects with HER2-mutant NSCLC, 88 with HER2-overexpressing NSCLC, 338 with HER2-positive BC, and 242 with HER2-positive GC.	
Population Characteristics	General	Age: median 61.0 (range: 20.0-96.0) Sex: 261 (34.1%) males, 504 (65.9%) females ECOG PS: 357 (46.7%) 0, 407 (53.2%) 1, 1 (0.1%) 2 Race-country: 284 (37.1%) Asian from Japan, 95 (12.4%) Asian not from Japan, 386 (50.5%) non-Asian Albumin: median 39.0 (range: 22.0-55.0)	
	Pediatrics (if any)	Not applicable	
Dose(s) Included		0.8, 1.6, 5.4, 6.4, 7.4, and 8.0 mg/kg	
Exposure Metrics Explored (range)		AUC and Cmin for Cycle 1, Cavg over first 2 cycles, Cavg in the dosing interval at steady state and Cavg up to the endpoint (e.g., ORR) for T-DXd	
Covariates Evaluated		Age, albumin, baseline tumor size, HER2extra cellular domain, HER2 IHC, HER2 mutation type, ECOG PS, prior checkpoint inhibitor use, brain metastasis, lung metastasis, and number of prior systemic therapies	
Final Model Parameters		Summary	Acceptability [FDA's comments]
Model Structure		ORR: logistic regression BTR: linear model SoD time course: tumor growth inhibition model (Claret model). Details are only described for ORR, other models are described in the ER report.	
Model Parameter Estimates		Applicant - Table	

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Model Evaluation	Applicant - Figure 20	
Covariates and Clinical Relevance	ORR: baseline tumor size, baseline albumin, prior checkpoint inhibitor use and Race (Asian from Japan)	
Simulation for Specific Population	Simulations were conducted to predict ORR in subjects with HER2-mutant NSCLC at 5.4 mg/kg and 6.4 mg/kg doses. The predicted response rate in the HER2-mutant NSCLC population was 56.4% (90% CI: 47.6, 64.8) at the 5.4 mg/kg dose compared to 57.6% at the 6.4 mg/kg dose (90% CI: 49.2, 65.8).	
Visualization of ER relationships	Applicant - Figure 21	
Overall Clinical Relevance for ER	The ER relationship for efficacy endpoints showed that T-DXd systemic exposures correlated with ORR, BTR as well as time course of SoD. These analyses predicted clinically meaningful efficacy at the 6.4 and 5.4 mg/kg doses in HER2-mutant NSCLC population and the difference in efficacy endpoints between 6.4 mg/kg and 5.4 mg/kg doses was not predicted to be clinically meaningful among subjects with HER2-mutant NSCLC.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	

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Applicant - Table 41: Parameter Estimates from Final ER Model of ORR (Partial Pooling)

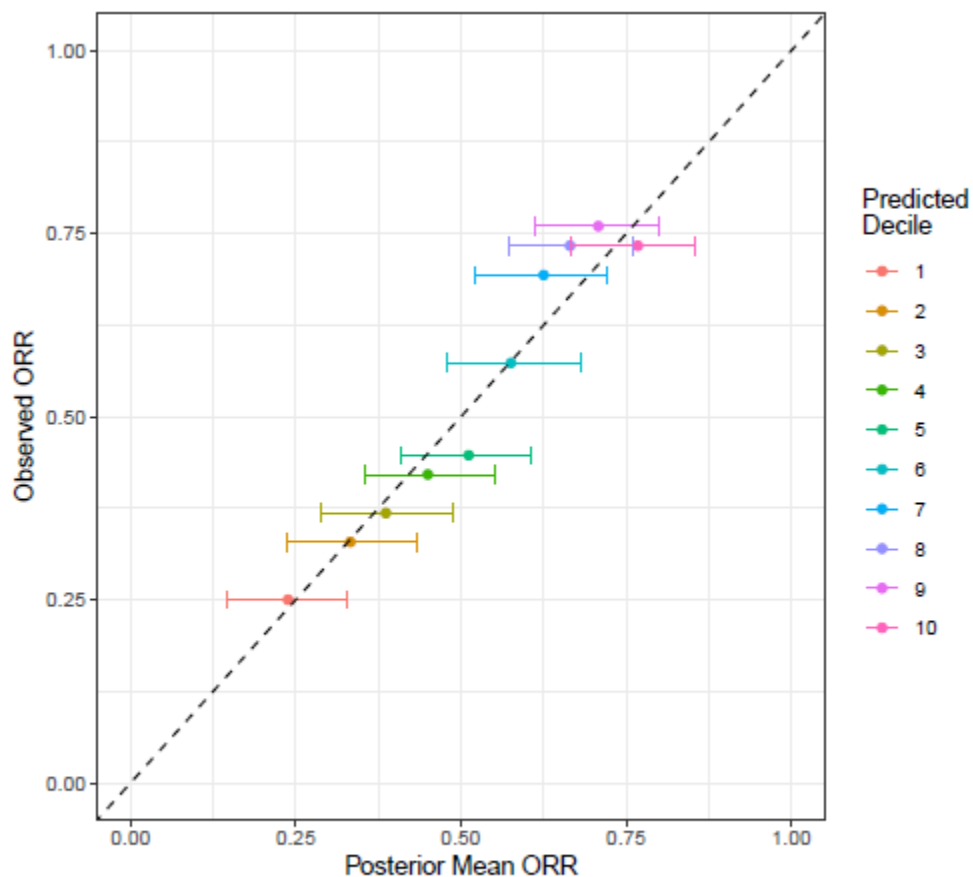
Parameter	Median	95% CI	Rhat	ESS Bulk	ESS Tail
Structural model parameters					
α_1 Intercept for HER2 mutant NSCLC	-0.351	(-0.799, 0.0923)	1.00	2980	2640
α_2 Intercept for HER2 overexpressing NSCLC	-1.12	(-1.62, -0.647)	1.00	4600	3190
α_3 Intercept for Breast	0.602	(0.308, 0.887)	1.00	3670	3110
α_4 Intercept for Gastric	-0.296	(-0.721, 0.124)	1.00	4330	3060
β_1 E-R slope for HER2 mutant NSCLC (1/ng/mL)	1.22e-05	(-1.56e-06, 2.71e-05)	1.00	6080	3170
β_2 E-R slope for HER2 overexpressing NSCLC (1/ng/mL)	1.33e-05	(-1.81e-06, 3.04e-05)	1.00	4670	3220
β_3 E-R slope for Breast (1/ng/mL)	1.27e-05	(-1.42e-06, 2.79e-05)	1.00	5900	3250
β_4 E-R slope for Gastric (1/ng/mL)	1.18e-05	(-3.32e-06, 2.70e-05)	1.00	5160	3160
Covariate effect parameters					
γ_1 Effect of Time Since Diagnosis in NSCLC (1/months)	-0.00564	(-0.0150, 0.00328)	1.00	2250	2710
γ_2 Effect of Prior Checkpoint Inhibitor	0.514	(0.163, 0.866)	1.00	3970	2880
γ_3 Effect of Log Baseline Sum of Diameters (1/log(cm))	0.231	(0.0217, 0.431)	1.00	5970	3000
γ_4 Effect of Baseline Albumin (1/g/L)	0.0564	(0.0252, 0.0877)	1.00	4920	2990
γ_5 Effect of Race-Country (Asian from Japan)	0.362	(0.0706, 0.664)	1.00	4960	3140
γ_6 Effect of Race-Country (Asian not from Japan)	-0.0759	(-0.464, 0.329)	1.00	4940	3110
γ_7 Effect of Baseline ECOG PS (0 vs 1+)	0.125	(-0.149, 0.393)	1.00	4710	2850
γ_8 Effect of Liver Metastases (Yes vs No)	-0.298	(-0.575, -0.0286)	1.00	5030	2880
γ_9 Effect of Time Since Diagnosis in Breast cancer (1/months)	-0.00205	(-0.00495, 0.000865)	1.00	4470	3370
γ_{10} Effect of Time Since Diagnosis in Gastric cancer (1/months)	0.00706	(-0.00363, 0.0178)	1.00	5520	3290
γ_{11} Effect of Time Since Diagnosis in HER2 overexpressing NSCLC (1/months)	0.00572	(-0.00817, 0.0190)	1.00	6750	3180

Source: ER Efficacy Report.

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Applicant - Figure 20: ORR Model: Decile Calibration

Intervals are 90% prediction intervals, and the dashed line is the predicted=observed line.



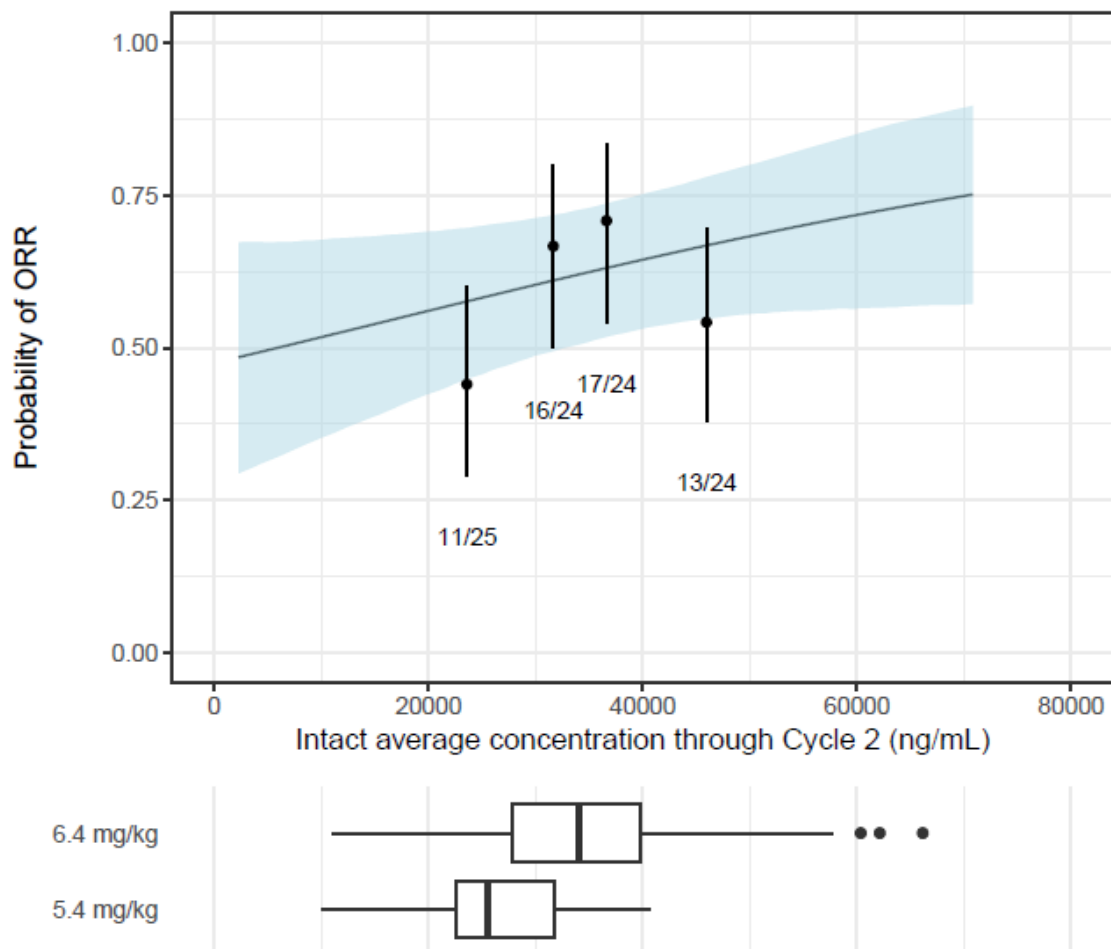
Source code: orr_cavg_model.Rmd
Source graphic: decile_calibration_plot_report.pdf

Source: ER Efficacy Report.

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Applicant - Figure 21: ORR Model: Exposure Effect with the Partial Pooling Model

Intervals are 90% prediction and confidence intervals, and the boxplots are the distributions of exposures



Source: ER Efficacy Report.

ER (safety) Executive Summary

The FDA's Assessment:

In support of the dosing recommendations for this BLA, the applicant also submitted reports of exposure-response (E-R) for safety analyses to update previous E-R models with updated data from patients with NSCLC from Studies U204 and new data from Study U206 to characterize E-R for safety relationships. The E-R for safety results indicated that there is a positive E-R relationship for any AEs grade $\geq$

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3 and any serious AE with PK exposure - DXd Cavg to the time of event in the pooled population across all evaluated doses. The E-R between AUCss and ILD any grade incidence also showed a positive relationship. The updated E-R for safety results are generally in line with prior ER analyses.

In summary, the applicant's E-R analysis for safety showed statistically significant E-R relationships between PK exposures and safety endpoints, including T-DXd steady state AUC was correlated with Any Grade ILD, DXd Cavg to the event time was correlated with Grade 3 AEs and serious AEs. Overall, Applicant's E-R for safety analysis appears adequate to support proposed lower dosing regimen of 5.4 mg/kg Q3W.

ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Update E-S relationships for the AEs listed below Evaluate covariate relationships to explain potential differences in efficacy or safety among subgroups of patients Integrate PopPK and E-S analyses to support dose selection in NSCLC patients
Study Included		J101, J102, A103, A104, U201, J202, U205, and U204
Population Included		BC, gastric/GEJ cancer, NSCLC, and other
Endpoint		AEs associated with study drug discontinuation, AEs associated with dose reduction, AEs associated with study drug interruption, ≥Grade 3 AE, SAEs, anemia (any grade and ≥Grade 3), neutropenia (any grade and ≥Grade 3), thrombocytopenia (any grade and ≥Grade 3), adjudicated drug-related ILD (any grade and ≥Grade 3), LVEF decrease based on echocardiogram/multigates acquisition (any grade and ≥Grade 2)
No. of Patients (total, and with individual PK)		N = 1059
Population Characteristics	General	Age: median 60.0 yrs (range: 20.0-96.0) Weight: median 59.6 kg (range: 27.3-125)

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(Applicant - Table)		Sex: 344 (32.5%) male, 715 (67.5%) female								
	Organ impairment	Renal (CrCL using Cockcroft-Gault equation): 41.3% normal function, 41.1% mild impairment, 17.4% moderate impairment, and 0.3% severe impairment								
	Pediatrics (if any)	Not applicable								
	Geriatrics (if any)	Included: age range: 20.0-96.0								
Dose(s) Included		0.8, 1.6, 3.2, 5.4, 6.4, 7.4, and 8.0 mg/kg								
Exposure Metrics Explored (range)		Cmax, Cmin, and AUC for Cycle 1 and at steady-state and CavgTOE (accounting for any dose reductions or interruptions) for T-DXd and DXd								
Covariates Evaluated		Race-country, baseline age, baseline body weight, sex, baseline ECOG PS, HER2 status, HER2-mutant status, HER2 IHC, baseline albumin, baseline AST, baseline total bilirubin, renal function, liver metastases at baseline, lung metastases at baseline, number of prior nonhormonal cancer therapies, prior treatment with checkpoint inhibitors, baseline platelets, baseline hemoglobin, baseline neutrophils, pneumonectomy, lung comorbidities at baseline, and oxygen saturation.								
Final Model Parameters		<table><tr><th>Summary</th><th>Acceptability [FDA's comments]</th></tr><tr><td>Model Structure For ILD (any grade and ≥Grade 3): Cox regression models For other safety endpoints: logistic regression models</td><td></td></tr><tr><td>Model Parameter Estimates Applicant - Table Applicant - Table Parameters for other exposure-safety models are presented in the report.</td><td></td></tr><tr><td>Model Evaluation Applicant - Figure 22 Applicant - Figure 23</td><td></td></tr></table>	Summary	Acceptability [FDA's comments]	Model Structure For ILD (any grade and ≥Grade 3): Cox regression models For other safety endpoints: logistic regression models		Model Parameter Estimates Applicant - Table Applicant - Table Parameters for other exposure-safety models are presented in the report.		Model Evaluation Applicant - Figure 22 Applicant - Figure 23	
Summary	Acceptability [FDA's comments]									
Model Structure For ILD (any grade and ≥Grade 3): Cox regression models For other safety endpoints: logistic regression models										
Model Parameter Estimates Applicant - Table Applicant - Table Parameters for other exposure-safety models are presented in the report.										
Model Evaluation Applicant - Figure 22 Applicant - Figure 23										

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	Model evaluation for other exposure-safety models are presented in the report.	
Covariates and Clinical Relevance	Any grade ILD: Race-country, line of therapy, baseline CrCL Grade ≥3 ILD: Baseline albumin, oxygen saturation Grade ≥3 AEs: Baseline albumin, baseline body weight, pneumonectomy SAEs: ECOG PS, baseline albumin, baseline CrCL, race-country	
Simulation for Specific Population	Model-predicted AE rates were generally comparable between HER2-mutant and HER2-overexpressing NSCLC subjects at the 6.4 mg/kg dose, except for 12% higher SAEs for HER2-overexpressing subjects. Model-predicted AE rates were lower (up to 8%) following the T-DXd 5.4 mg/kg Q3W regimen compared with T-DXd 6.4 mg/kg Q3W in NSCLC subjects. Modeled rates of ILD at 180 days were higher (~2.5% to 5%) following the T-DXd 6.4 mg/kg Q3W regimen in NSCLC subjects compared with T-DXd 5.4 mg/kg Q3W in BC or NSCLC subjects.	
Visualization of ER relationships	Applicant - Figure 22 Applicant - Figure 23 Visualization for other exposure-safety models are presented in the report.	
Overall Clinical Relevance for ER	Results from the ER analysis for safety were generally consistent with the observed safety profile and indicated there was a correlation between T-DXd and DXd exposures and safety endpoints. These analyses support an acceptable safety profile in NSCLC subjects at 5.4 mg/kg and 6.4 mg/kg Q3W T-DXd doses relative to 5.4 mg/kg Q3W T-DXd in BC, and a numerically	

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	better safety profile at the 5.4 mg/kg dose relative to the 6.4 mg/kg Q3W dose in NSCLC.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	

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NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-XXX)

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Applicant - Table 42: Summary of Baseline Characteristics and Laboratory Values in the Dataset

Covariate	DS8201-A-J101 (N=286)	DS8201-A-J102 (N=51)	DS8201-A-A103 (N=12)	DS8201-A-A104 (N=40)	DS8201-A-U201 (N=250)	DS8201-A-J202 (N=169)	DS8201-A-U205 (N=76)	DS8201-A-U204 (N=175)	Overall (N=1059)
Age (yr)									
Median [Min, Max]	58.0 [23.0, 83.0]	56.0 [31.0, 79.0]	54.5 [36.0, 69.0]	57.0 [31.0, 80.0]	56.0 [28.0, 96.0]	65.0 [29.0, 82.0]	61.5 [20.0, 77.0]	62.0 [29.0, 88.0]	60.0 [20.0, 96.0]
Body weight (kg)									
Median [Min, Max]	58.1 [34.6, 125]	51.5 [38.9, 75.2]	60.0 [51.0, 68.0]	55.8 [41.3, 90.7]	59.7 [37.9, 121]	57.0 [27.3, 109]	74.9 [41.9, 121]	64.6 [39.7, 110]	59.6 [27.3, 125]
Albumin (g/L)									
Median [Min, Max]	38.0 [23.0, 50.0]	40.0 [28.0, 48.0]	41.5 [31.0, 47.0]	41.0 [31.0, 49.0]	41.0 [22.0, 50.0]	35.0 [23.0, 48.0]	40.0 [25.0, 48.0]	41.0 [27.0, 55.0]	39.0 [22.0, 55.0]
AST (U/L)									
Median [Min, Max]	30.0 [10.0, 170]	28.0 [15.0, 103]	21.5 [16.0, 63.0]	24.5 [12.0, 82.0]	32.0 [13.0, 189]	27.0 [11.0, 123]	24.0 [11.0, 120]	20.0 [9.00, 133]	27.0 [9.00, 189]
Total Bilirubin (μmol/L)									
Median [Min, Max]	8.55 [3.42, 28.2]	10.3 [5.13, 23.9]	9.15 [6.67, 12.5]	8.55 [5.13, 18.8]	7.00 [3.00, 56.0]	8.55 [2.57, 34.2]	7.66 [1.00, 22.7]	5.00 [1.50, 20.0]	7.00 [1.00, 56.0]
Hemoglobin (g/L)									
Median [Min, Max]	116 [77.0, 150]	118 [93.0, 147]	119 [90.0, 140]	128 [97.0, 157]	120 [53.0, 163]	107 [79.0, 151]	120 [82.0, 160]	122 [83.0, 161]	117 [53.0, 163]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	3 (0.3%)
Neutrophils (x 10 ⁹ /L)									
Median [Min, Max]	3.78 [1.38, 73.7]	2.96 [1.31, 6.16]	4.09 [2.06, 7.66]	3.60 [1.60, 12.5]	3.38 [0.710, 15.8]	4.05 [1.15, 20.0]	4.58 [2.20, 12.6]	4.51 [1.31, 16.6]	3.83 [0.710, 73.7]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	4 (0.4%)
Platelets (x 10 ⁹ /L)									

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation (BLA 761139/S-XXX)

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Median [Min, Max]	226 [95.0, 751]	217 [106, 346]	267 [154, 410]	234 [124, 510]	197 [73.0, 585]	221 [101, 656]	237 [85.0, 656]	266 [118, 878]	229 [73.0, 878]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)	0 (0%)	0 (0%)	1 (0.6%)	5 (0.5%)
Oxygen saturation (%)									
Median [Min, Max]	98.0 [88.0, 100]	98.0 [95.0, 100]	97.0 [93.0, 98.0]	98.0 [93.0, 100]	97.0 [88.0, 100]	98.0 [93.0, 100]	98.0 [95.0, 100]	97.0 [88.0, 100]	98.0 [88.0, 100]
Missing	10 (3.5%)	1 (2.0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	1 (1.3%)	0 (0%)	14 (1.3%)
Sex									
Female	224 (78.3%)	51 (100%)	12 (100%)	22 (55.0%)	250 (100%)	41 (24.3%)	21 (27.6%)	94 (53.7%)	715 (67.5%)
Male	62 (21.7%)	0 (0%)	0 (0%)	18 (45.0%)	0 (0%)	128 (75.7%)	55 (72.4%)	81 (46.3%)	344 (32.5%)
Race-country									
Asian from Japan	176 (61.5%)	51 (100%)	0 (0%)	31 (77.5%)	52 (20.8%)	134 (79.3%)	0 (0%)	36 (20.6%)	480 (45.3%)
Asian not from Japan	14 (4.9%)	0 (0%)	12 (100%)	9 (22.5%)	49 (19.6%)	35 (20.7%)	3 (3.9%)	9 (5.1%)	131 (12.4%)
Non-Asian	96 (33.6%)	0 (0%)	0 (0%)	0 (0%)	149 (59.6%)	0 (0%)	73 (96.1%)	130 (74.3%)	448 (42.3%)
Baseline renal Impairment									
Normal	125 (43.7%)	23 (45.1%)	5 (41.7%)	19 (47.5%)	121 (48.4%)	48 (28.4%)	36 (47.4%)	60 (34.3%)	437 (41.3%)
Mild	119 (41.6%)	23 (45.1%)	7 (58.3%)	17 (42.5%)	96 (38.4%)	72 (42.6%)	28 (36.8%)	73 (41.7%)	435 (41.1%)
Moderate	41 (14.3%)	5 (9.8%)	0 (0%)	4 (10.0%)	33 (13.2%)	49 (29.0%)	12 (15.8%)	40 (22.9%)	184 (17.4%)
Severe	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	3 (0.3%)
ECOG PS									
0	177 (61.9%)	31 (60.8%)	3 (25.0%)	21 (52.5%)	143 (57.2%)	83 (49.1%)	27 (35.5%)	41 (23.4%)	526 (49.7%)
1	109 (38.1%)	20 (39.2%)	9 (75.0%)	19 (47.5%)	106 (42.4%)	86 (50.9%)	49 (64.5%)	134 (76.6%)	532 (50.2%)
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Tumor Type									
BC	182 (63.6%)	51 (100%)	12 (100%)	17 (42.5%)	250 (100%)	0 (0%)	0 (0%)	0 (0%)	512 (48.3%)
GC	47 (16.4%)	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)	169 (100%)	76 (100%)	0 (0%)	293 (27.7%)
NSCLC	18 (6.3%)	0 (0%)	0 (0%)	6 (15.0%)	0 (0%)	0 (0%)	0 (0%)	175 (100%)	199 (18.8%)
Other	39 (13.6%)	0 (0%)	0 (0%)	16 (40.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	55 (5.2%)

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Primary tumor location									
Gastric	39 (13.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	146 (86.4%)	27 (35.5%)	0 (0%)	212 (20.0%)
GEJ	8 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (13.6%)	49 (64.5%)	0 (0%)	80 (7.6%)
Unknown	239 (83.6%)	51 (100%)	12 (100%)	40 (100%)	250 (100%)	0 (0%)	0 (0%)	175 (100%)	767 (72.4%)
Total gastrectomy									
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	32 (18.9%)	0 (0%)	0 (0%)	32 (3.0%)
No	239 (83.6%)	51 (100%)	12 (100%)	39 (97.5%)	250 (100%)	137 (81.1%)	76 (100%)	175 (100%)	979 (92.4%)
Unknown	47 (16.4%)	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	48 (4.5%)
Lung metastases									
Yes	107 (37.4%)	11 (21.6%)	3 (25.0%)	22 (55.0%)	136 (54.4%)	54 (32.0%)	25 (32.9%)	54 (30.9%)	412 (38.9%)
No	179 (62.6%)	40 (78.4%)	9 (75.0%)	18 (45.0%)	114 (45.6%)	115 (68.0%)	51 (67.1%)	121 (69.1%)	647 (61.1%)
Liver metastases									
Yes	117 (40.9%)	28 (54.9%)	0 (0%)	0 (0%)	72 (28.8%)	89 (52.7%)	47 (61.8%)	41 (23.4%)	394 (37.2%)
No	169 (59.1%)	23 (45.1%)	12 (100%)	40 (100%)	178 (71.2%)	80 (47.3%)	29 (38.2%)	134 (76.6%)	665 (62.8%)
Number non-hormone prior therapies									
≥5	180 (62.9%)	16 (31.4%)	3 (25.0%)	9 (22.5%)	165 (66.0%)	10 (5.9%)	11 (14.5%)	0 (0%)	394 (37.2%)
<5	106 (37.1%)	35 (68.6%)	9 (75.0%)	31 (77.5%)	85 (34.0%)	159 (94.1%)	65 (85.5%)	175 (100%)	665 (62.8%)
Prior checkpoint inhibitor									
Yes	13 (4.5%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)	58 (34.3%)	6 (7.9%)	0 (0%)	81 (7.6%)
No	273 (95.5%)	51 (100%)	12 (100%)	40 (100%)	246 (98.4%)	111 (65.7%)	70 (92.1%)	51 (29.1%)	854 (80.6%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	124 (70.9%)	124 (11.7%)
HER2 Status									
Negative	67 (23.4%)	47 (92.2%)	0 (0%)	8 (20.0%)	1 (0.4%)	44 (26.0%)	0 (0%)	0 (0%)	167 (15.8%)
Positive	184 (64.3%)	4 (7.8%)	12 (100%)	23 (57.5%)	249 (99.6%)	123 (72.8%)	75 (98.7%)	0 (0%)	670 (63.3%)
Mutant	11 (3.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	88 (50.3%)	99 (9.3%)
Over Expressing	7 (2.4%)	0 (0%)	0 (0%)	6 (15.0%)	0 (0%)	0 (0%)	0 (0%)	87 (49.7%)	100 (9.4%)
Missing	17 (5.9%)	0 (0%)	0 (0%)	3 (7.5%)	0 (0%)	2 (1.2%)	1 (1.3%)	0 (0%)	23 (2.2%)
HER2 IHC									
0	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (4.1%)	0 (0%)	1 (0.6%)	10 (0.9%)

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1+	36 (12.6%)	37 (72.5%)	0 (0%)	7 (17.5%)	2 (0.8%)	21 (12.4%)	0 (0%)	2 (1.1%)	105 (9.9%)
2+	79 (27.6%)	12 (23.5%)	1 (8.3%)	11 (27.5%)	38 (15.2%)	37 (21.9%)	10 (13.2%)	31 (17.7%)	219 (20.7%)
3+	136 (47.6%)	2 (3.9%)	11 (91.7%)	18 (45.0%)	210 (84.0%)	101 (59.8%)	65 (85.5%)	11 (6.3%)	554 (52.3%)
Missing	33 (11.5%)	0 (0%)	0 (0%)	4 (10.0%)	0 (0%)	3 (1.8%)	1 (1.3%)	130 (74.3%)	171 (16.1%)
Pneumonectomy									
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	39 (22.3%)	39 (3.7%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	136 (77.7%)	136 (12.8%)
Missing	286 (100%)	51 (100%)	12 (100%)	40 (100%)	250 (100%)	169 (100%)	76 (100%)	0 (0%)	884 (83.5%)
Line of therapy									
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	76 (100%)	175 (100%)	251 (23.7%)
3	286 (100%)	51 (100%)	12 (100%)	40 (100%)	250 (100%)	169 (100%)	0 (0%)	0 (0%)	808 (76.3%)

Notes: For continuous variables, values reflect median value and range. For categorical variables, values reflect count and percent of total subjects per study. Total gastrectomy is categorized as “yes”, “no”, or “missing” for subjects with GC but always “no” for other cancers. Normal renal function, mild impairment, moderate impairment, and severe impairment were defined as creatinine clearance (using Cockcroft and Gault equation) of ≥ 90 mL/min, ≥ 60 to < 90 mL/min, ≥ 30 to < 60 mL/min, and < 30 mL/min, respectively. Line of therapy 2 refers to second line or later; line of therapy 3 refers to third line or later. The cutoff for the number of non-hormone prior therapies was set to the cutoff used in the prior BC analysis, which was the median value.

Source: ER Safety Report.

Enhertu[®] (fam-trastuzumab deruxtecan-nxki)*Applicant - Table 43: Any Grade ILD Final Model Parameters*

ER Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd AUC steady state (µg/mL×day)	Any Grade ILD	Slope	0.00146	0.000303	21
		Creatinine clearance (mL/min)	−0.00767	0.00282	37
		Non-Asian	−0.556	0.179	32
		Asian not from Japan	−0.992	0.352	35
		Second line or later	0.423	0.196	46

Source: ER Safety Report

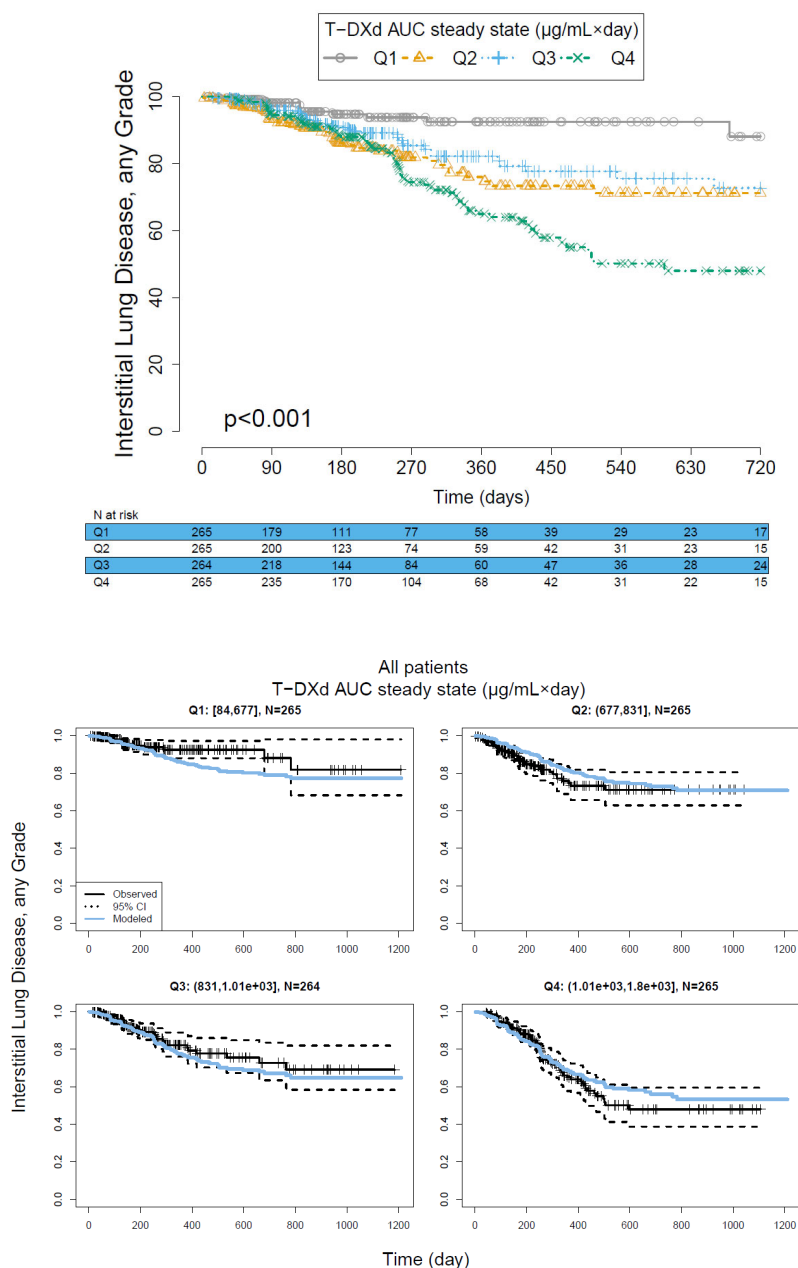
Applicant - Table 44: Grade ≥3 ILD Final Model Parameters

ER Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade ≥3 ILD	Slope	0.0206	0.00504	24
		Albumin (g/L)	−0.114	0.0379	33
		Oxygen saturation (%)	−0.245	0.0711	29

Source: ER Safety Report

Applicant - Figure 22: Kaplan-Meier Curves with Univariate Cox Regression Fit for Any Grade ILD for AUC exposure quartiles

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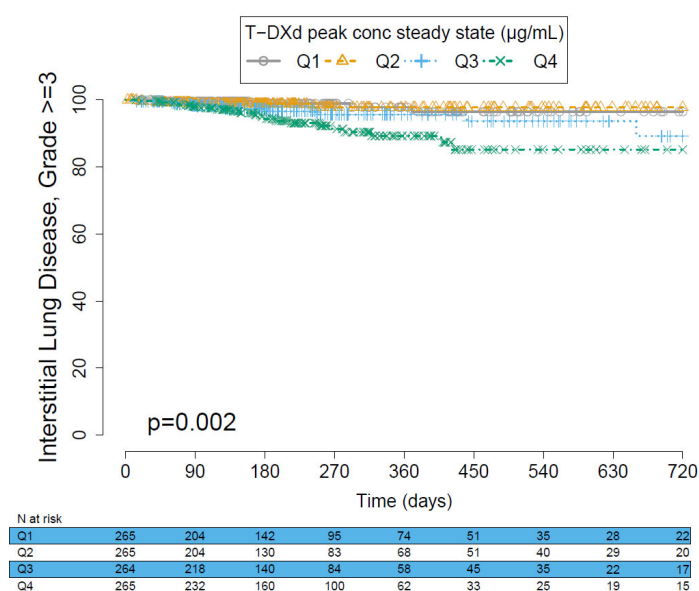


Note: The top plot presents Kaplan Meier curves by exposure quartiles. P-value in the top plot is for the log-rank test. The bottom 4 plots present univariate Cox regression fits per exposure quartile. The exposure metric and exposure quartile are indicated in the title of each plot. The solid black line represents the estimated Kaplan-Meier curves. The dashed lines are 95% CIs. The solid blue line represents the estimated Kaplan-Meier curve determined with univariate Cox regression.

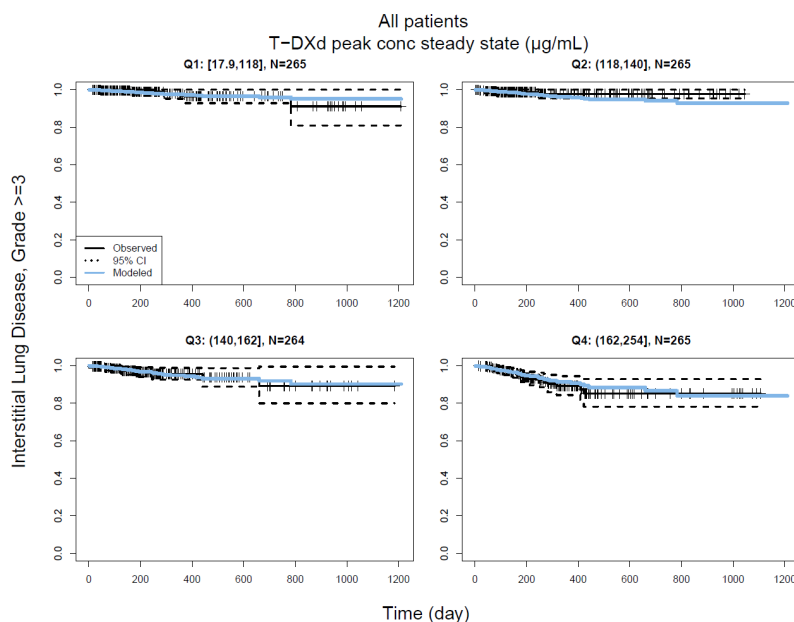
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Source: ER Safety Report

Applicant - Figure 23: Kaplan-Meier Curves with Univariate Cox Regression Fit for Grade ≥3 ILD for Steady State Peak Concentration Exposure Quartiles



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Note: The top plot presents Kaplan Meier curves by exposure quartiles. P-value in the top plot is for the log-rank test. The bottom 4 plots present univariate Cox regression fits per exposure quartile. The exposure metric and exposure quartile are indicated in the title of each plot. The solid black line represents the estimated Kaplan-Meier curves. The dashed lines are 95% CIs. The solid blue line represents the estimated Kaplan-Meier curve determined with univariate Cox regression.

Source: ER Safety Report

The FDA's Assessment:

In general, the applicant's ER analysis for T-DXd and DXd is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

ER Review Issues

In support of this BLA, the applicant submitted topline reports of exposure-response (E-R) for efficacy analyses. Applicant's Exposure-response analyses for efficacy updated an existing model of ORR in the HER2-mutant NSCLC population with updated efficacy data from Study U204 (DCO date 3 Dec 2021) and newly available efficacy data from Study U206 (DCO date 24 Mar 2022) and prior data from HER2-mutant NSCLC subjects from Study J101. The pooled population included 181 HER2-mutant NSCLC subjects with available ORR data: 11 from Study J101 (all at T-DXd 5.4 mg/kg Q3W), 91 from U204 (all at T-DXd 6.4 mg/kg Q3W), and 79 from U206 (51 at T-DXd 5.4 mg/kg Q3W and 28 at T-DXd 6.4 mg/kg Q3W).

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Q3W). The analysis dataset included 59 males and 118 females with a median age of 60 years (23 to 88 years old) and a median body weight of 62 kg (39.7 to 111 kg).

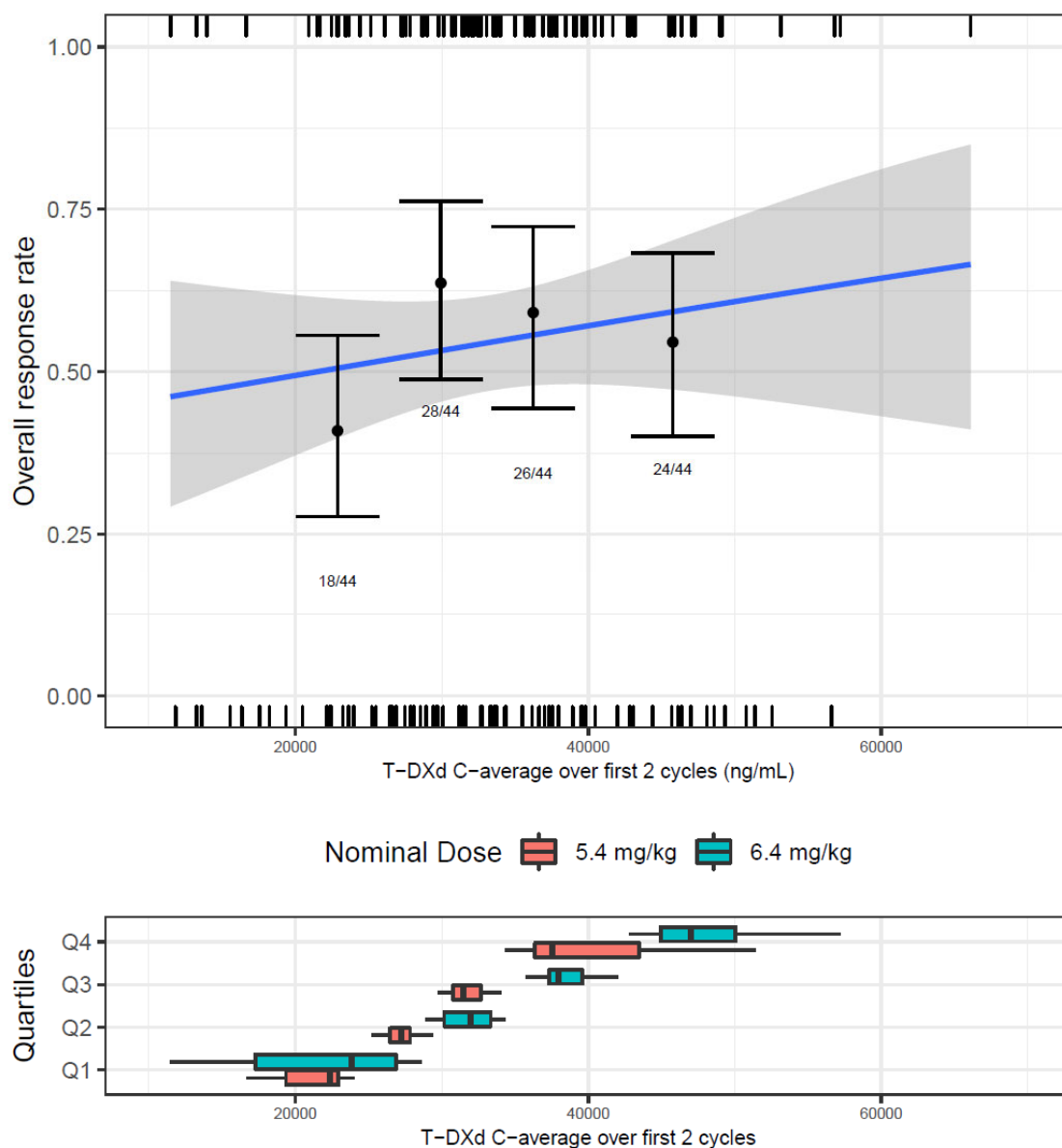
The primary efficacy endpoint for E-R analyses is the ORR. An updated population PK model was used to calculate exposure values for subjects (see section **Population PK Analysis**). C_{avg} , Cycle2 was used as the exposure metric in an ORR model. The E-R analysis for efficacy results showed T-DXd exposure had a positive but shallow relationship with ORR (see FDA - Figure 24). Various prognostic factors were examined in the ORR model. Among these, race-country (Asian (93 subjects, 52.5%), 30.5% of subjects reported as White, and the remaining subjects as Other), baseline tumor size (typically 58 mm, 10.3 to 178 kg) were identified as statistically significant covariates with T-DXd exposure. The model showed that Asian subjects were associated with higher ORRs than non-Asian subjects; subjects with larger baseline target tumor size were associated with lower ORRs than subjects with smaller baseline target tumor size, and subjects with larger baseline target tumor size were also associated with

lower exposure. And the updated E-R results are generally consistent with prior ER analyses conducted using data from NSCLC subjects from Studies J101 and U204 (Applicant - Figure 20, Applicant - Figure 21).

The applicant's E-R analysis for efficacy appears adequate. The updated E-R results showed a flat E-R relationship for efficacy endpoints, which may imply that the effectiveness of T-DXd reached a plateau, which supports the proposed dosage of 5.4 mg/kg Q3W.

FDA - Figure 24. Applicant's update E-R Analysis for ORR vs PK Exposure $C_{avg, cycle 2}$

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Dashed line along the x-axis indicates responder (one) and non-responder (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that are responders within each quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion. Numbers represent responders and total subjects within each quartile. Plot excluded one subject with exposure value greater than 100,000 ng/mL. Bottom panel shows distribution of exposure by quartile within each nominal dose of HER2-mutant NSCLC population.

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Source: Applicant's ER Topline Efficacy Report titled Update of Exposure-Response Analysis of Efficacy of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer, Report Number: DSI1501F-EE-BriefComm-v1.0-Final, Figure 3.

In support of the dosing recommendations of this BLA, the applicant also submitted reports of exposure-response (E-R) for safety analyses to update previous E-R models with updated data from patients with NSCLC from Studies U204 and new data from Study U206 to characterize E-R for safety relationships for the following AE endpoints: occurrence of any AE, Grade ≥ 3 , occurrence of any serious AE, time to first occurrence of drug-related adjudicated interstitial lung disease (ILD) AE, any grade.

The primary data sources for E-R for safety (ES) included 11 studies (Studies J101, J102, A103, A104, U201, J202, U205, U302, U303, U204, and U206). The safety endpoints and related covariates were listed in the Error! Reference source not found.. In total, the pooled population included 1850 subjects with available ILD data. The new Study (Study U206) introduced 147 subjects to this safety analysis. The E-R for safety results indicated that the a positive E-R relationship for any AEs grade ≥ 3 (FDA - Figure 25) and any serious AE (FDA - Figure 26) with PK exposure - DXd Cavg to the time of event in the pooled population across all evaluated doses. The E-R between AUCss and ILD any grade incidence also showed a positive relationship (FDA - Figure 27), and survival analysis showed shorter ILD any grade event-free survival was associated with higher AUCss exposure (FDA - Figure 28). The updated E-R for safety results are generally in line with prior ER analyses results (Applicant - Table , Applicant - Table , Applicant - Figure 22, Applicant - Figure 23).

In summary, Applicant's E-R analysis for safety showed statistically significant E-R relationships between PK exposures and safety endpoints. This includes the findings that T-DXd steady state AUC was correlated with Any Grade ILD, DXd Cavg to the event time was correlated with Grade 3 AEs and serious AEs. Overall, Applicant's E-R analysis for safety appears adequate to support proposed lower dosing regimen of 5.4 mg/kg Q3W.

FDA - Table 45. Exposure Metrics and Covariates to be considered for Exposure-Safety models

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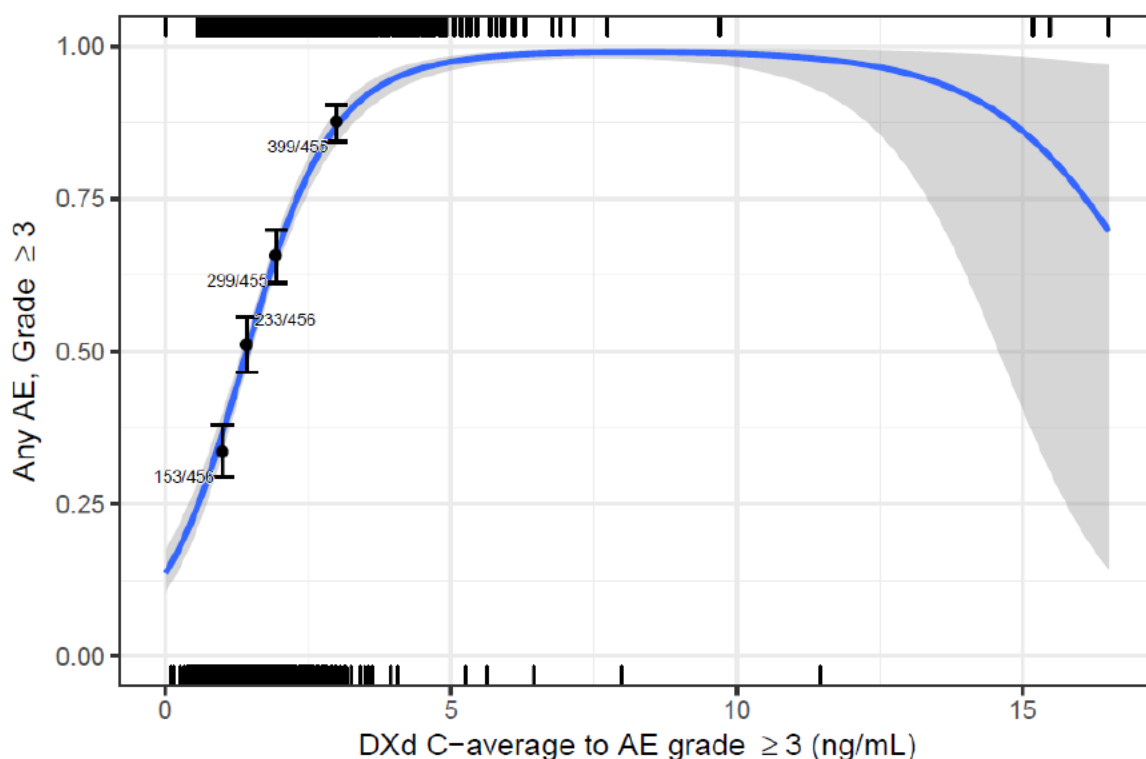
Safety Endpoint	Exposure Metric	Model Covariates
AE grade ≥ 3 (binary)	DXd C_{avg}	bodyweight*, albumin, prior CDK4/6 inhibitor, <i>tumor type / HER2 status*, prior treatment with checkpoint inhibitor*</i>
Any serious AE (binary)	DXd C_{avg}	race-country*, Eastern Cooperative Oncology Group (ECOG) performance status (PS)*, creatinine clearance (CRCL)*, albumin, <i>tumor type / HER2 status*, prior treatment with checkpoint inhibitor*</i>
ILD, any grade (time-to-first event)	T-DXd area under the concentration-time curve at steady state (AUC_{ss})	CRCL, race-country, oxygen saturation, <i>tumor type / HER2 status*, prior treatment with checkpoint inhibitor*</i>

Covariates not identified by the previous analysis are italicized. Covariates that interact with exposure are indicated with an asterisk. In all cases, average concentration (C_{avg}) refers to average concentration to the time of event.

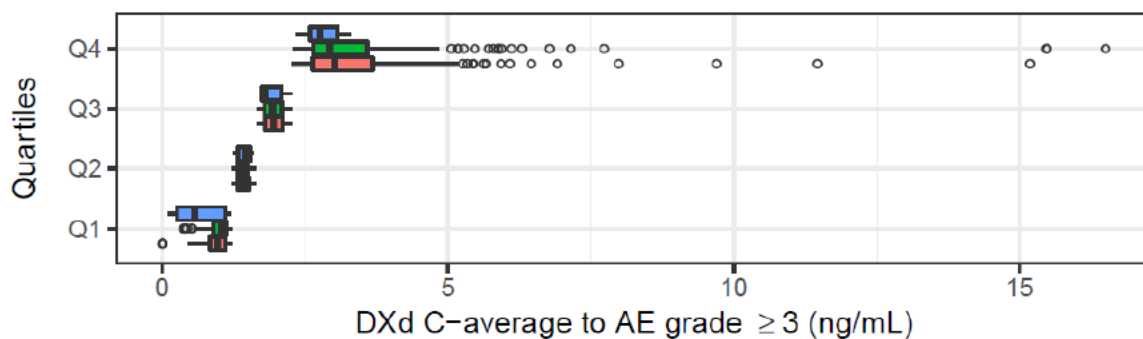
Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Table 1.

FDA - Figure 25. ES analysis of any AE, Grade ≥ 3 : observed and model-fitted rate of AE associated with Dxd C_{avg} through the time of first event

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Nominal Dose 5.4 mg/kg 6.4 mg/kg Other



Dashed line along the x-axis indicates ILD any grade event (one) and no event (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that have event within each quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion. Numbers represent responders and total subjects within each quartile.

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Version date: July 2021 (ALL NDA/ BLA reviews)

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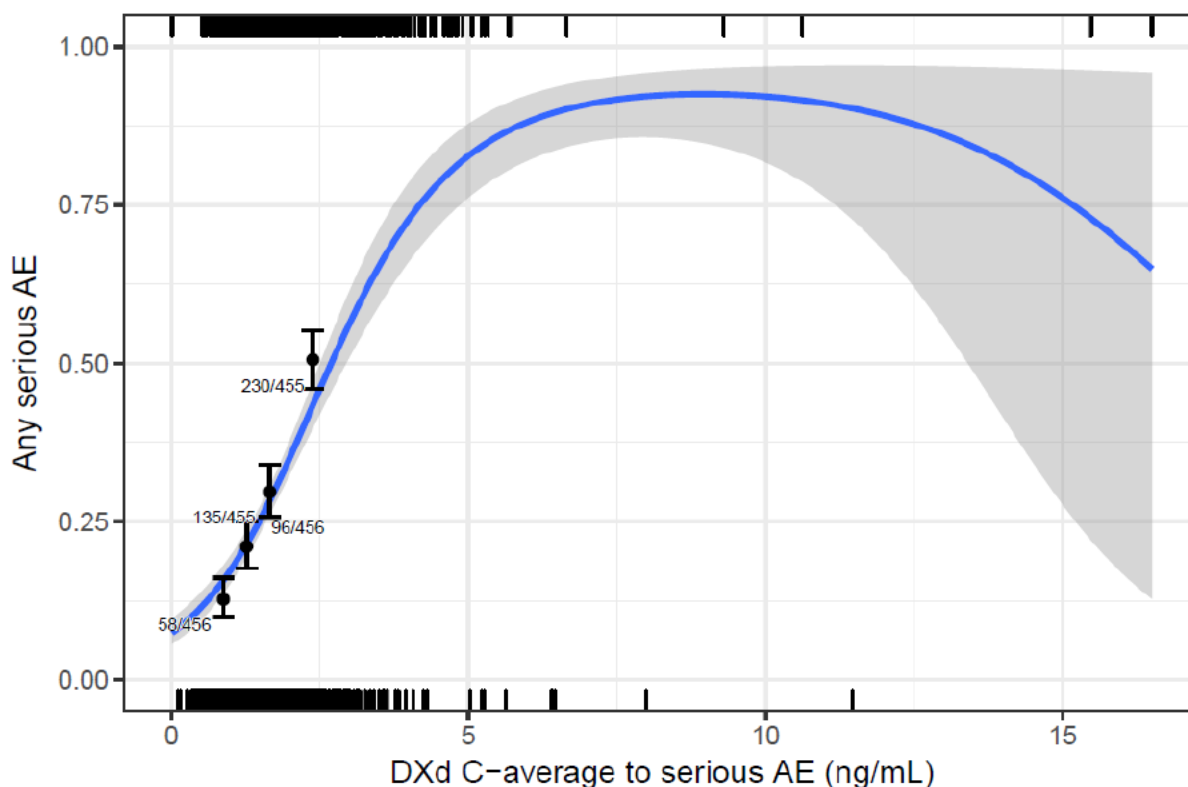
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Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors, Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 2.

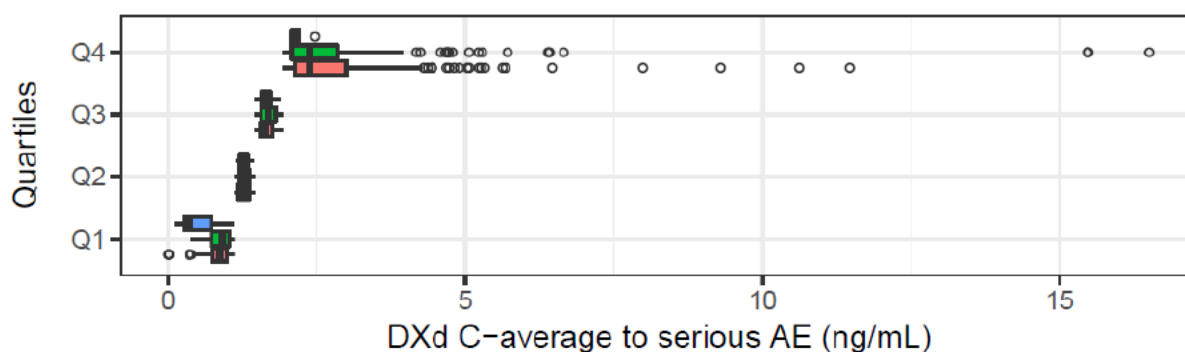
FDA - Figure 26. ES analysis of serious AE: observed and model-fitted rate of AE associated with Dxd Cavg through the time of first event.

APPEARS THIS
WAY ON
ORIGINAL

Enhertu® (fam-trastuzumab deruxtecan-nxki)



Nominal Dose 5.4 mg/kg 6.4 mg/kg Other



Dashed line along the x-axis indicates ILD any grade event (one) and no event (zero) subjects. Solid blue line represents a smooth (univariate generalized additive model (GAM)) of the original data, and the grey region indicates a 95% confidence interval of smoothed relationship. Points are the proportion of subjects that have event within each quartile, plotted at the category midpoints. Error bars are 95% confidence interval of proportion.

Enhertu® (fam-trastuzumab deruxtecan-nxki)

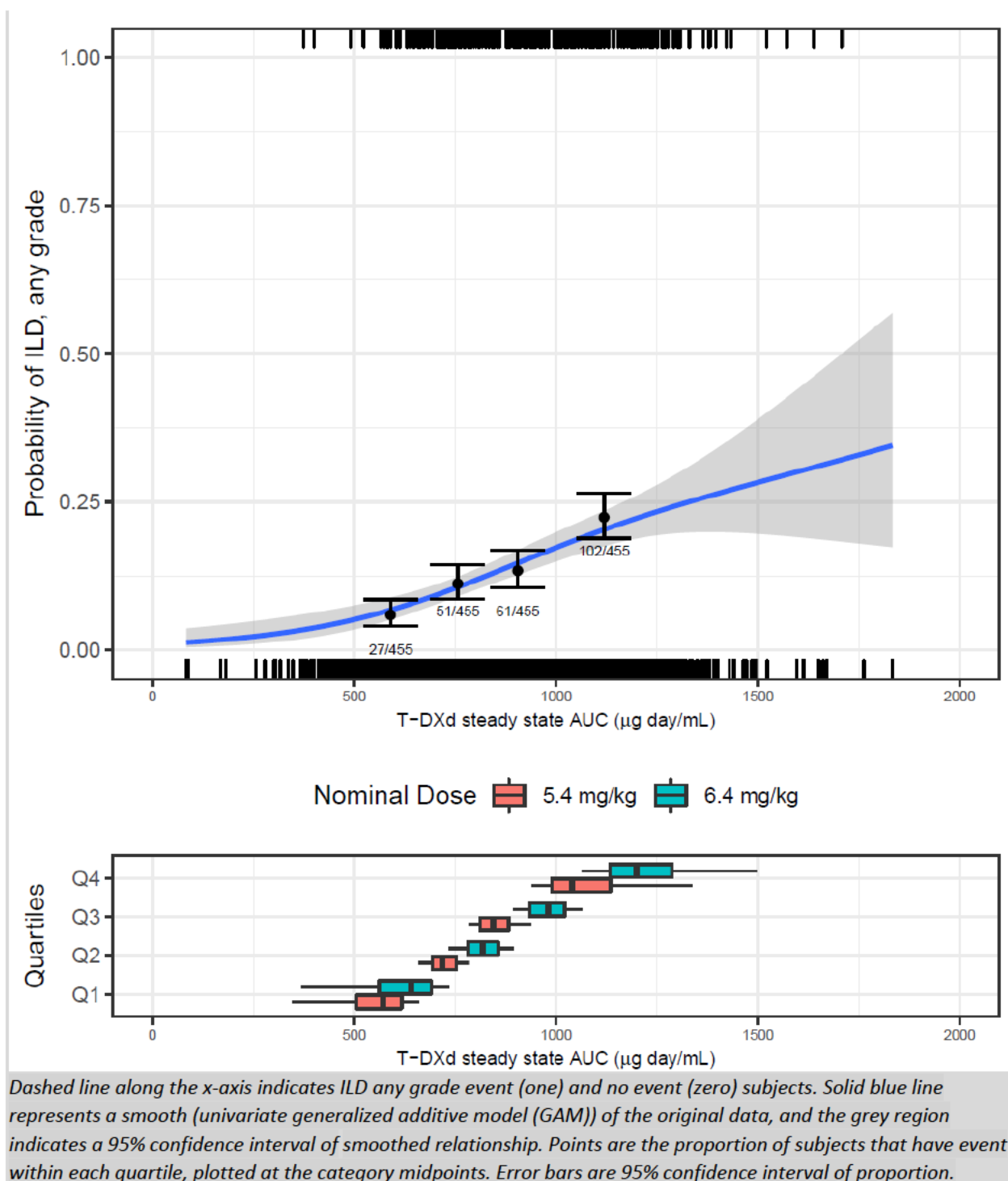
Numbers represent responders and total subjects within each quartile.

Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 11.

FDA - Figure 27. Safety Endpoint - ILD Any Grade Incidence versus PK Exposure - AUCss.

APPEARS THIS WAY
ON ORIGINAL

Enhertu® (fam-trastuzumab deruxtecan-nxki)



Enhertu[®] (fam-trastuzumab deruxtecan-nxki)

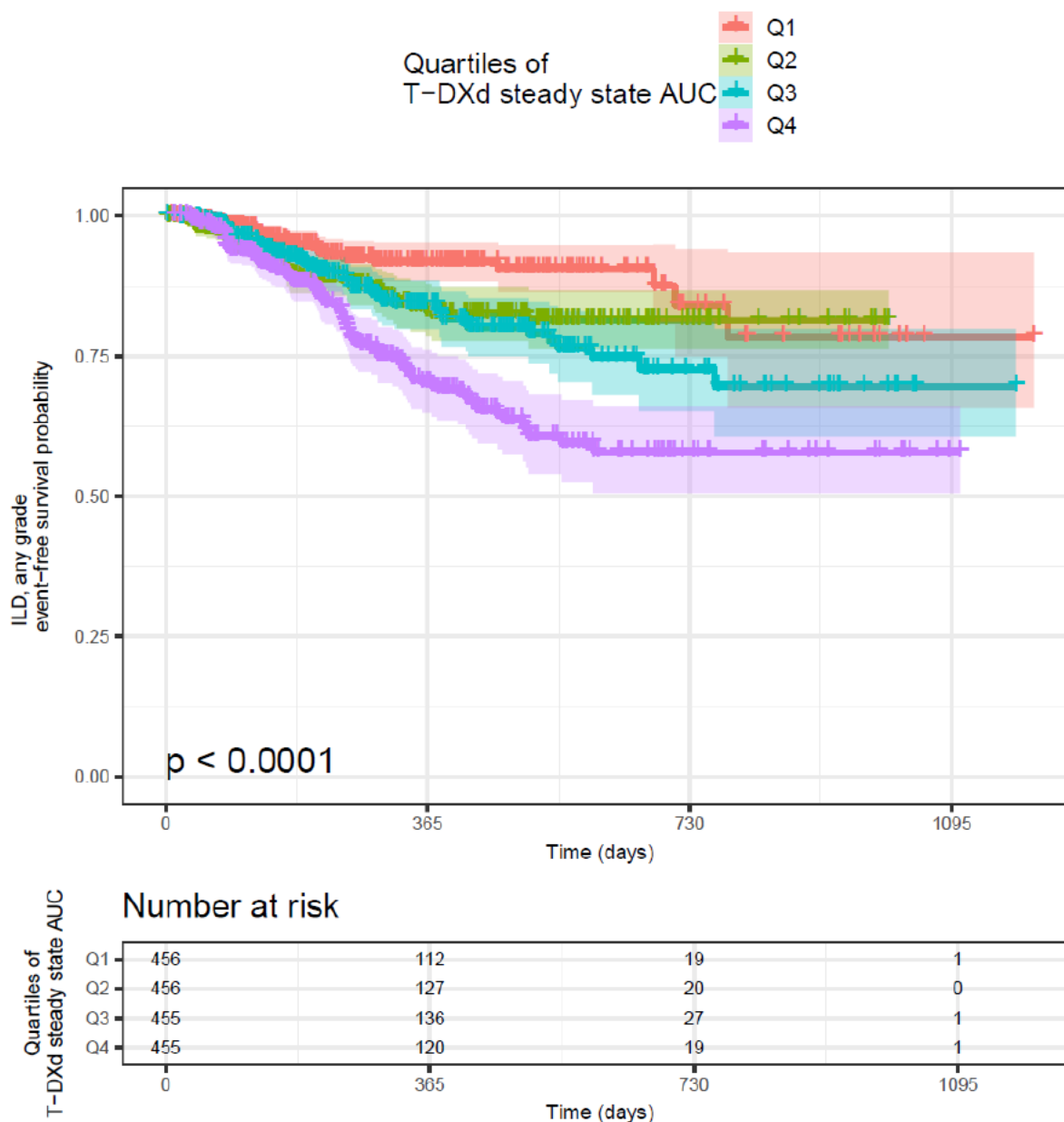
Numbers represent responders and total subjects within each quartile. Plot excluded two subjects with exposure value greater than 2,000 μ day/mL. Bottom panel shows distribution of exposure by quartile for subjects receiving T-DXd T-DXd 5.4 mg/kg Q3W or T-DXd 6.4 mg/kg Q3W.

Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors, Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 2.

FDA - Figure 28. Kaplan-Meier curve of ILD Any Grade Event-Free Survival for Different Quartiles of AUCss.

APPEARS THIS
WAY ON
ORIGINAL

Enhertu® (fam-trastuzumab deruxtecan-nxki)



Kaplan-Meier curve of ILD any grade event-free survival for different quartiles (colors) of continuous predictor.

Shaded area is 95% confidence interval of relationship. Number represents p-value of log-rank test.

Enhertu® (fam-trastuzumab deruxtecan-nxki)

Source: Applicant's ER Topline Safety report titled Update of Exposure-Response Analysis of Safety of Trastuzumab Deruxtecan in Patients with Non-Small Cell Lung Cancer and Other Solid Tumors, Report Number: DSI1501F-ES-BriefComm-v1.0-Final, Figure 20

Reviewer's Independent Analysis

None.

Overall Benefit-Risk Evaluation Based on ER Analyses

The Applicant's Position:

The ER analysis supported the clinically meaningful efficacy of T-DXd in the HER2-mutant NSCLC population and a generally acceptable safety profile at the T-DXd 6.4 mg/kg dose.

The FDA's Assessment:

In general, the applicant's updated ER analysis for T-DXd and DXd is considered acceptable for the purpose of supporting analyses objectives. Overall, Applicant's updated PPK and E-R for safety and efficacy analyses appear adequate to support proposed lower dosing regimen of 5.4 mg/kg Q3W.

19.5 ADDITIONAL SAFETY ANALYSES CONDUCTED BY FDA

The FDA's Assessment:

[FDA will complete this section.]

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Reviewer	Gautam Mehta, M.D.	CDER/OOD/DO2	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 19.1, 19.2	Select one: ☒ Authored ☐ Approved
Signature: Gautam U. Mehta -S Digitally signed by Gautam U. Mehta -S Date: 2022.08.05 17:41:57 -04'00'				
Clinical Team Leader	Paz Vellanki, M.D., Ph.D.	CDER/OOD/DO2	Sections:	Select one: ☒ Authored ☒ Approved
Signature: See Cross-Disciplinary Team Lead				
Statistical Reviewer	Yi Ren, Ph.D.	CDER/OTS/DBV	Sections: 8, 9	Select one: ☒ Authored ☐ Approved
Signature: Yi Ren -S Digitally signed by Yi Ren -S Date: 2022.08.05 22:52:38 -04'00'				
Acting Statistical Team Leader	Anup Amatya, Ph.D.	CDER/OTS/DBV	Sections: 8.1, 8.3, 9	Select one: ☒ Authored ☒ Approved
Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2022.08.09 11:57:17 -04'00'				
Supervisory Mathematical Statistician (OB/DBV)	Pallavi Mishra-Kalyani, Ph.D.	CDER/OTS/DBV	Sections:	Select one: ☐ Authored ☒ Approved
Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2022.08.08 13:27:12 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst, Ph.D.	CDER/OND/OOD/DHOT	Sections:	Select one: ☐ _x_ Authored ☐ _x_ Approved
Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S Date: 2022.08.06 07:17:55 -04'00'				
Nonclinical Team leader	Claudia Miller, Ph.D.	CDER/OND/OOD/DHOT	Sections	Select one: ☒ _x_ Authored ☐ _x_ Approved
Signature: Claudia Miller -S Digitally signed by Claudia Miller Date: 2022.08.10 09:52:47 -04'00'				
Clinical Pharmacology Reviewer	Lili Pan, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ _x_ Authored ☐ _x_ Approved
Signature: Lili Pan -S Digitally signed by Lili Pan -S Date: 2022.08.08 21:02:09 -04'00'				
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ _x_ Authored ☒ _x_ Approved
Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2022.08.09 08:09:18 -04'00'				
Pharmacometrics Reviewer	Yuzhuo Pan, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ _x_ Authored ☐ _x_ Approved
Signature: Yuzhuo Pan -S Digitally signed by Yuzhuo Pan -S Date: 2022.08.08 21:29:33 -04'00'				
Pharmacometrics Team Leader	Jiang Liu, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ _x_ Authored ☒ _x_ Approved
Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.08.08 22:55:48 -04'00'				

Genomics Reviewer	Sarah Dorff, Ph.D.	CDER/OTS/OCP/DTPM	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2022.08.09 10:12:58 -04'00'			
Genomics Team Leader	Robert Schuck, Ph.D.	CDER/OTS/OCP/DTPM	Sections: 6	Select one: ☒ Authored ☒ Approved
	Signature: Robert Schuck -S Digitally signed by Robert Schuck -S Date: 2022.08.09 07:11:10 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, Ph.D.	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.08.09 11:33:44 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OND/OOD/DOII	Sections:	Select one: ☐ X Authored ☐ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2022.08.08 13:22:31 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Paz Vellanki, M.D., Ph.D.	CDER/OOD/DO2	Sections:	Select one: ☐ X Authored ☐ X Approved
	Signature: Paz J. Vellanki -S Digitally signed by Paz J. Vellanki -S Date: 2022.08.10 00:06:39 -04'00'			
Division Director (Signatory)	Harpreet Singh, M.D.		Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Bonnie H. Moore -S Digitally signed by Bonnie H. Moore -S Date: 2022.08.10 10:32:51 -04'00'			

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/

GAUTAM U MEHTA
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B HARPREET SINGH
08/11/2022 02:45:33 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

CLINICAL REVIEW(S)

CLINICAL REVIEW OF SUPPLEMENTAL BIOLOGICS LICENSE APPLICATION

BLA number:	761139
Supplement number:	21
Applicant:	Daiichi Sankyo
Drug Name:	Fam-trastuzumab deruxtecan-nxki (ENHERTU)
Reviewer:	Gautam Mehta
Team Leader:	Paz Vellanki

The clinical review team recommends accelerated approval for fam-trastuzumab deruxtecan-nxki for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer whose tumors have an activating HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy. For additional details of the review, refer to the Assessment Aid.

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/s/

GAUTAM U MEHTA
08/10/2022 02:56:08 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

PRODUCT QUALITY REVIEW(S)

Memorandum of Assessment

Submission Tracking Number (STN):	BLA 761139, supplement 21 (SN0184 and SN 0189)
Subject:	PAS (Efficacy Supplement): treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.
Stamp Date:	January 18, 2022, and February 16, 2022 (rolling submission)
Review Date:	June 23, 2022
Primary Assessor:	Davinna Ligons, CDER/OPQ/OBP/DBRR III
Secondary Assessor:	Frances Namuswe, CDER/OPQ/OBP/DBRR III
Tertiary Assessor:	Maria Gutierrez Lugo, CDER/OPQ/OBP/DBRR III
RBPM:	Raniya Al-Matari
Applicant:	Daiichi Sankyo, Inc
Product:	Enhertu (fam-trastuzumab deruxtecan-nxki)
Action Due Date:	July 28, 2022

I. SUMMARY BASIS OF RECOMMENDATION:

A. Recommendation:

I recommend approval of this supplement from an immunogenicity assay perspective. No approvability issues were identified with respect to the validation and performance of the immunogenicity assays used during the clinical studies. We defer to the clinical and clinical pharmacology review teams for assessment of the immunogenicity clinical data and the adequacy of the changes to labeling. The Applicant's proposed categorical exclusion for MAAL-9001 based on 21 CFR 21.35(c) is acceptable. We defer to OLDP for the request of categorical exclusion for DXd (MAAA-1181a).

II. ASSESSMENT

A. Product Introduction

Enhertu/fam-trastuzumab deruxtecan (also known as DS-8201a) is an antibody-drug conjugate (ADC) composed of a recombinant humanized anti-human epidermal growth factor receptor (anti-HER) 2 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) covalently conjugated to a topoisomerase 1 inhibitor drug-linker (D-L), MAAA-1162a. The mAb component, referred to as MAAL-9001, has the same amino acid sequence as trastuzumab and binds specifically to the human HER2 extracellular domain. The released drug, MAAA-1181a, inhibits topoisomerase I and leads to apoptosis of the target cells.

DS-8201a drug product (DP) is a single-use sterile lyophilized powder containing 100 mg of DS-8201a in a (b) (4) glass vial sealed with a rubber stopper and flip-off crimp cap. Prior to use, DS-8201a DP is reconstituted with 5 mL of water for injection to provide a solution with a concentration of 20

mg/mL DS-8201a in (b) (4) histidine buffer that contains 90 mg/mL sucrose and (b) (4) of polysorbate 80 at a pH of 5.5.

A dose of 5.4 mg/kg of Enhertu is currently approved 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 and a dose of 6.4 mg/kg is approved for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

B. Scope of Changes

In supplement 21, Daiichi proposes to add the indication non-small cell lung cancer with a dose of (b) (4) of ENHERTU every three weeks until disease progression or unacceptable toxicity. Table 3.1 below summarizes the clinical studies used to evaluate PK, safety, efficacy, and immunogenicity.

Table 3.1: Studies Included in the Population Pharmacokinetics, Immunogenicity, and Exposure-Response Analyses

Studies Included in PopPK and E-R Safety Analyses	Studies Included in E-R Efficacy Analysis	Studies Included in Immunogenicity Analysis
J101, J102, A103, A104, U201, J202, U204, U205	J101, U201, J202, U204, U205	J101, J102, A103, A104, U201, J202, U204, U205, U302

E-R = exposure-response; PopPK = population pharmacokinetic

J101 = Study DS8201-A-J101; J102 = Study DS8201-A-J102; A103 = Study DS8201-A-A103;

A104 = Study DS8201-A-A104; U201 = Study DS8201-A-U201; J202 = Study DS8201-A-J202;

U204 = Study DS8201-A-U204; U205 = Study DS8201-A-U205; U302 = Study DS8201-A-U302

The proposed edits to the labeling including section 6.2 Immunogenicity were provided on May 18, 2022 (SN 0215). Below summarizes the Sponsor's proposed edits to section 6.2 of the labeling.

6.2 Immunogenicity



The table below list the ADA and neutralizing antibody (NAb) assays and validation reports used to evaluate the immunogenicity clinical samples and the bioanalytical reports that summarizes the clinical immunogenicity data and performance of the assays during the clinical study.

ADA detection and NAb assays	Clinical Studies
REFG2: Electrochemiluminescent Method for the Detection of Anti-DS-8201a Antibodies in Human Serum. Project dated May 2020. (method #ICDIM 213), (b) (4)	DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201, DS8201-A-J202, DS8201-A-U205, DS8201-A-U204, DS8201-A-U302
RIRM2: Cell-Based Method for the Detection of Neutralizing Antibodies to DS-8201a in Human Serum (method # VSDCBA 82), (b) (4)	
8393-529: Immunoassay method for Detection, Confirmation, and Titration of Anti-DS-8201a Antibodies Human Serum using Electrochemiluminescent (ECL) (method ICSH 19-020), (b) (4)	ADA detection and NAb binding assays for analysis of clinical samples collected in mainland China subjects in the breast cancer clinical studies U302.
8423-462: Validation of a Cell Based Method for Determination of Neutralization Anti-Drug Antibodies to DS-8201a in Human Serum.	

Assessor comment: All ADA detection, neutralization, and titter assays are adequately validated. The assessment memos for the RIRM2, 8393-529, and 8423-462 method validation reports were being finalized at the time of completing this review memo for supplement 21. Refer to the immunogenicity review memo for PMC 3762-16 for assessment and information regarding RIRM2, 8393-529, and 8423-462 validation reports, and updates to the REFG2 validation report. Refer to the immunogenicity review

memo dated June 2019 by Zhenzhen Liu for assessment of the original REFG2 method validation report. This review assesses the performance of the assays during clinical testing.

The table below summarizes the bioanalytical reports and immunogenicity results of the clinical study and performance of the ADA assays during the clinical study. The IR dated May 25, 2022 provides hyperlinks to the clinical bioanalytical reports for the ADA and NAb assay results for the nine clinical studies indicated in the Table below.

Clinical Studies and Performance of Assays during Clinical Studies	
Study No.	Bioanalytical Reports for ADA and NAb Assays
DS8201-A-J101 Phase 1, two-part, non-randomized, open label, multiple-dose, first-in-human study of T-DXd, in subjects with advanced solid malignant tumors	ADA detection assay: report# RFGN (BLA 761139/S-011 (SN 0130), Module 5.3.5.3 Integrated Report for ADA Assay Revision). <i>Comment: Thirty-four runs were conducted for the RFGN study and seven of the runs failed due to failure of the controls. 124 runs were conducted for the RFGN2 study and 21 of the runs failed due to failure of the controls. The success rate is ~80% and is acceptable.</i> NAb assay: report # ROPO (BLA 761139/S-017/20 (SN 0178), Module 5.3.1.4, Combined Nab Assay Sample Analysis Report for DS-8201a Studies) <i>Comment: All clinical runs passed the acceptance criteria.</i>
DS8201-A-J102 Phase 1, multicenter, open-label, multiple -dose study of T-DXd to assess the effect on the QT interval and PK in subjects with HER2 expressing metastatic and/or unresectable breast cancer	ADA detection assay: report# RIZM (BLA 761139/S-011 (SN 0130), Module 5.3.5.3 Integrated Report for ADA Assay Revision) <i>Comment: Twenty clinical runs were conducted for the screening, confirmatory, and titer assessments, and all runs passed the acceptance criteria.</i> NAb assay: report# ROPP

	(BLA 761139/S-017/20 (SN 0178), Module 5.3.1.4, Combined Nab Assay Sample Analysis Report for DS-8201a Studies) <i>Comment: One clinical run was conducted, and the run passed the acceptance criteria.</i>
DS8201-A-A103 Phase 1, multicenter, open-label study of T-DXd to assess safety and PK in subjects with HER2-positive advanced and/or refractory gastric, gastroesophageal junction adenocarcinoma, or breast cancer	ADA detection assay: report# RJMS (BLA 761139/S-011 (SN 0130), Module 5.3.5.3 Integrated Report for ADA Assay Revision) <i>Comment: four clinical runs were conducted for the screening, and confirmatory assessments, and all runs passed the acceptance criteria.</i> NAb assay: report# ROPM (BLA 761139/S-017/20 (SN 0178), Module 5.3.1.4, Combined Nab Assay Sample Analysis Report for DS-8201a Studies) <i>Comment: One clinical run was conducted, and it passed the acceptance criteria.</i>
DS8201-A-A104 A Phase 1, multicenter, open-label, single sequence crossover study to evaluate drug -drug interaction potential of OATP1B/CYP3A inhibitor on the pharmacokinetics of T-DXd in subjects with HER2-expressing advanced solid malignant tumors	ADA detection assay: report# RJES (BLA 761139/S-011 (SN 0130), Module 5.3.5.3 Integrated Report for ADA Assay Revision) <i>Comment: Eleven clinical runs were conducted for the screening, confirmatory, and titer assessment, and all runs passed the acceptance criteria.</i> NAb assay: report# ROPN (BLA 761139/S-017/20 (SN 0178), Module 5.3.1.4, Combined Nab Assay Sample Analysis Report for DS-8201a Studies)

	<i>Comment: One clinical run was conducted and passed the acceptance criteria.</i>
DS8201-A-U201 A Phase 2, multicenter, open-label study of T-DXd, an anti-HER2-ADC for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1	ADA detection assay: report# RINY (BLA 761139/S-011 (SN 0130), Module 5.3.5.3 Integrated Report for ADA Assay Revision) <i>Comment: 71 clinical runs were conducted, and ten runs failed due operator or analyst error, abnormal raw data response, or controls not meeting acceptance criteria. The success rate was ~85% and is acceptable.</i> NAb assay: report# ROPQ (BLA 761139/S-017/20 (SN 0178), Module 5.3.1.4, Combined Nab Assay Sample Analysis Report for DS-8201a Studies) <i>Comment: A total of four clinical runs were conducted, and two of the did not pass the acceptance criteria due failed controls. The performance of the assay is acceptable.</i>
DS8201-A-J202 A Phase 2, Multicenter, Open-Label Study of T-DXd in Subjects with HER2-Expressing Advanced Gastric or Gastroesophageal Junction Adenocarcinoma	ADA detection assay: report# RIZG (BLA 761139/S-011 (SN 0130), Module 5.3.5.1 DS8201-A-J202 CSR Appendix 16-1-13) <i>Comment: Seventy-four runs were conducted for the screening, confirmatory, and titer assays combined. Seven of the clinical runs failed due to failure of the positive and negative controls. There was a ~91% success rate and the performance of the assay is acceptable.</i> NAb assay: report# RPHH (Module 5.3.1.4 Clinical Study Report (CSR) Appendix 16.1.13 Study Bioanalysis Report)

	<i>Comment: Four clinical runs were conducted, and one run was aborted. The performance of the assay is acceptable.</i>
DS8201-A-U204 A Phase 2, Multicenter, Open-Label, 2-Cohort Study of T-DXd for HER2- Over-Expressing or -Mutated, Unresectable and/or Metastatic Non- Small Cell Lung Cancer	ADA detection assay: report# RKIK (BLA 761139/S-021 (SN 0189), Module 5.3.5.2 DS8201-A-U204 CSR Appendix 16-1-13) <i>Comment: A total 111 clinical runs were conducted for the screening, confirmatory and titer assays and 9 runs failed. The success rate was >91% and is acceptable.</i> NAb assay: report# RPHL (BLA 761139/S-021 (SN0189), Module 5.3.5.2 DS8201-A-U204 CSR Appendix 16-1-13) Comments: Three clinical runs were conducted, and all runs passed the acceptance criteria.
DS8201-A-U205 Phase 2, Open-label, Single-arm Trial of T-DXd in HER2-positive, Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Subjects Who Have Progressed On or After a Trastuzumab-containing Regimen	ADA detection assay: report# RMPZ (Module 5.3.1.4 DS8201-A-U205 CSR Appendix 16-1-13) <i>Comment: Thirty-seven runs were conducted for the screening, confirmatory, and titer assays combined. Three of the clinical runs failed due to failure of the positive control or that the run was abandoned prior to completion. The success rate was >91% and is acceptable.</i> NAb assay: report# RPHI (Module 5.3.1.4 DS8201-A-U205 CSR Appendix 16-1-13) <i>Comments: Three clinical runs were conducted, and all runs passed the acceptance criteria.</i>
DS8201-A-U302	ADA detection assay: report# RKIG

A Phase 3, multicenter, randomized, open label, active-controlled study of T-DXd (DS-8201a), an anti-HER2 ADC, vs. T-DM1 for HER2-positive, unresectable and/or metastatic BC in subjects previously treated with trastuzumab and taxane	(BLA 761139/S-017/20 (SN 0178), Module 5.3.5.1 DS8201-A-U302 CSR Appendix 16-1-13) <i>Comment: A total 126 clinical runs were conducted for the screening, confirmatory and titer assessments, and 16 runs failed due to failure of controls, abnormal raw responses, or chemist error. The success rate was ~87% and is acceptable.</i> NAb assay: report# ROPS <i>Comments: Six clinical runs were conducted, and all runs pass the acceptance criteria.</i> <i>Additional comment: Clinical samples collected from mainland China were evaluated with the (b) (4) ADA assay 8393-529. A total nine clinical runs were conducted for the screening, and confirmatory assays and all runs passed the acceptance criteria. None of the samples confirmed positive and thus, no samples were evaluated for titer and neutralizing activity. (Refer to Bioanalytical Interim Report 03, Issue Date: September 10, 2021 (eCTD location: SN 0178, Module 5.3.5.1 Study Report Body Chapter, U302 16.1.13 Standalone Reports, page 1718))</i>
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No CMC related changes were reported in the current submission.

Labeling Assessor Comments:

Supplement 21 proposes to add the indication non-small cell lung cancer to the labeling. The Sponsor indicates that PK, safety, and efficacy data from clinical studies J101 and U204 are used to support the indication. The performance of the ADA and NAb assays in these clinical studies and across the various clinical studies are acceptable (refer to assessor comment above). The minor edit in section 6.2 of the labeling (b) (4) is acceptable because the reported ADA incidence is based on an integrated immunogenicity assessment made across 9 clinical studies (J101, J102, A103, A104, U201, J202, U204, U205, and U302) comprising patients with different solid tumors (refer to Supplement 17 immunogenicity review by Jun Liu dated March 24, 2022).

Environmental Assessment

Assessor comment:

The applicant provided an environmental analysis for Enhertu in section 1.12.14 of the current submission. Enhertu is an ADC comprised of a monoclonal antibody (MAAL-9001) conjugated with a drug-linker (MAAA-1162a), where the released drug is DXd (MAAA-1181a). The categorical exclusion for MAAL-9001 is based on 21CFR 21.35(c), as MAAL-9001 can be metabolized to amino acids in the body, are eliminated by either excretion or catabolism, and are considered naturally occurring in the environment. We defer to OLDP for the request of categorical exclusion for DXd (MAAA-1181a).



Davinna
Ligons

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Frances
Namuswe

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Maria
Gutierrez Lugo

Digitally signed by Maria Gutierrez Lugo

Date: 6/23/2022 04:43:18PM

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**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. NDA Supplement Number: BLA-761139-SUPPL-021

sNDA Recommendation: ☒ **Approval** ☐ Complete Response

sNDA managed by: ☐ OPQ ☒ OND

2. Submission(s) Being Reviewed:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	01/18/2022	01/18/2022	06/13/2022	08/16/2022	06/13/2022
		02/16/2022	02/16/2022			
Amendment		03/24/2022	03/24/2022			
		03/29/2022	03/29/2022			
		05/05/2022	05/05/2022			
		05/17/2022	05/17/2022			
		05/17/2022	05/17/2022			
		05/18/2022	05/18/2022			
		05/25/2022	05/25/2022			
		05/25/2022	05/25/2022			
		06/06/2022	06/06/2022			

3. Provides For:

Supplement 021 Proposed Indication:

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation and who have received a prior systemic therapy.

4. Review #: 01

5. Clinical Review Division: OOD/DO1

6. Name and Address of Applicant:

Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge, NJ, USA 07920

Contact: David Rusnak, JD Associate Director Regulatory Affairs Strategy

Phone: (b) (6)

Email: (b) (6)

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
ENHERTU (fam-trastuzumab deruxtecan-nxki)	Lyophilized powder	100 mg	IV	Rx	No

8. Chemical Name and Structure of Drug Substance:

Figure 1.1: Predicted Amino Acid Sequence of MAAL-9001

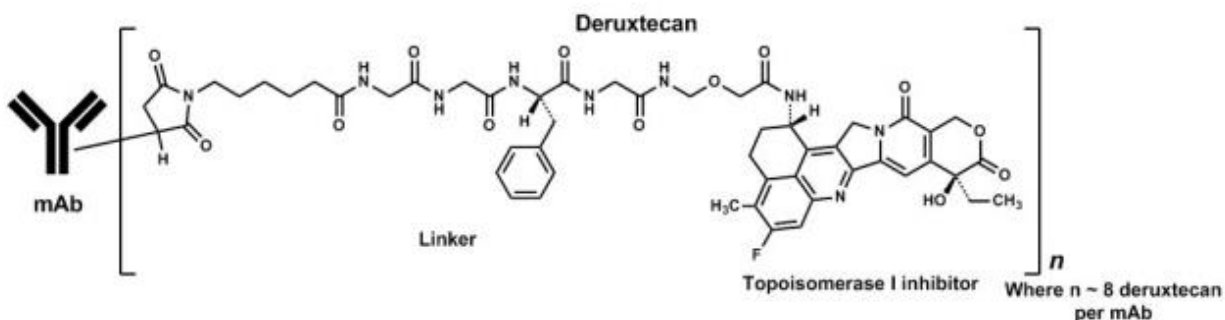
1	EVQLVESGGG	LVQPGGSLRL	SCAASGFNIK	DTYIHWVRQA	PGKGLEWVAR
51	IYPTNGYTRY	ADSVKGRFTI	SADTSKNTAY	LQMNSLRAED	TAVYYCSRWG
101	GDGFYAMDYW	GQGTLLTVSS	ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK
151	DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT
201	YICNVNHKPS	NTKVDKKVEP	KSCDKTHTCP	PCPAPELLGG	PSVFLFPPKP
251	KDTLMISRTP	EVTQVVDVVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN
301	STYRVSVSLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ
351	VYTLPPSREE	MTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTTPV
401	LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK
1	DIQMTQSPSS	LSASVGDRVT	ITCRASQDVN	TAVAWYQQKP	GKAPKLLIYS
51	ASFLYSGVPS	RFSGSRSGTD	FTLTISSLQP	EDFATYYCQQ	HYTTPPTFGQ
101	GTKVEIKRTV	AAPSVFIFPP	SDEQLKSGTA	SVVCLLNNFY	PREAKVQWKV
151	DNALQSGNSQ	ESVTEQDSKD	STYSLSSSTLT	LSKADYEKHK	VYACEVTHQG
201	LSSPVTKSFN	RGEC			

Residue for N-glycosylation (Asn³⁰⁰) is boxed.

CDR are represented by shaded line.

Disulfide bonds are represented by black lines.

*: Inter-chain disulfide bond between heavy chains



USAN: fam-trastuzumab deruxtecan-nxki

Laboratory code: MAAL-9001

Molecular Formula: see sequence above

Molecular Mass: (b) (4) Da not accounting for glycans

9. Indication:

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.

10. Supporting/Related Documents: None.

11. Consults: None.

12. Executive Summary:

Daiichi Sankyo Inc. has filed a BLA pursuant to 21 CFR 601.2 and section 351(a) of the Public Health Service (PHS) Act. ENHERTU (fam-trastuzumab deruxtecan-nxki; T-DXd) is a single use sterile lyophilized powder in a (b) (4) glass vial sealed with a (b) (4) (b) (4) rubber stopper and a (b) (4) aluminum yellow flip-off crimp cap. Prior to use, ENHERTU is reconstituted with 5 mL of water for injection to provide a solution with a drug substance concentration of 20 mg/mL, in (b) (4) histidine buffer that includes 90 mg/mL sucrose, (b) (4) of polysorbate 80 and a pH of 5.5. The reconstituted solution is a sterile solution for intravenous infusion. For administration, up to approximately 5 vials are used but the exact number of vials used varies depending on patient's weight. In support of this supplemental BLA (sBLA) for ENHERTU, a categorical exclusion from preparation of an environmental assessment (EA) is requested in accordance with the criteria set forth in 21 CFR §25.15, 21 CFR §25.31(b) 21 CFR §25.31 (c) being met. To the applicant's knowledge, no extraordinary circumstances exist (21 CFR §25.15(d)). The request for categorical exclusion is based on the calculation that was performed to show that the estimated concentration of the released drug (DXd), at the point of entry into the aquatic environment would be below 1 part per billion (ppb).

The expected introduction concentration (EIC) for ENHERTU in 2026 for the aquatic environment is calculated (according to the July 1998 FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologic Applications"). The EIC is (b) (4) of DXd. The estimated concentration of the released drug (DXd), at the point of entry into the aquatic environment would be below 1 part per billion (ppb). Therefore, the request for categorical exclusion may be granted.

There are no CMC related changes in these submissions.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Qi Liu., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ



Qi Charles
Liu

Digitally signed by Qi Charles Liu
Date: 6/13/2022 10:28:52AM
GUID: 53b4299e000120abe375af2240eda3f5



Ramesh
Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 6/13/2022 10:52:29PM
GUID: 502d0913000029f375128b0de8c50020

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: July 27, 2022

From: Stephanie L. Aungst, PhD

Pharmacology/Toxicology Reviewer

Division of Hematology Oncology Toxicology for Division of Oncology 2

Through: Claudia P. Miller, PhD

Acting Pharmacology/Toxicology Team Leader

Division of Hematology Oncology Toxicology for Division of Oncology 2

To: File for BLA 761139, Supplement 21

Re: Pharmacology and Toxicology

The primary nonclinical pharmacology/toxicology review is complete and has been added to the BLA Assessment Aid. My recommendation for this application is approval.

The secondary nonclinical pharmacology/toxicology review is complete. My recommendation for this application is approval.

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/s/

STEPHANIE L AUNGST
07/27/2022 02:20:10 PM

CLAUDIA P MILLER
07/27/2022 02:24:36 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA/BLA #:	BLA 761-139
Supplement #:	21
Drug Name:	Enhertu® (T-DXd, trastuzumab deruxtecan)
Indication(s):	Treatment of adult patients with unresectable or metastatic NSCLC whose tumors have a HER2 mutation and who have received a prior systemic therapy
Applicant:	Daiichi Sankyo
Date(s):	Receipt: Feb 16, 2022 PDUFA date: August 16, 2022
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yi Ren, Ph.D.
Concurring Reviewers:	Anup Amatya, Ph.D., Statistical Team Leader Pallavi Mishra-Kalyani, Ph.D., Supervisory Mathematical Statistician
Medical Division:	Division of Oncology Products 2
Clinical Team:	Gautam Mehta, M.D. Paz Vellanki, M.D., CDTL Harpreet Singh, M.D., Division Director
Project Manager:	Raniya Al-Matari

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which is available in DARRTS. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

YI N REN

08/26/2022 05:31:55 PM

ANUP K AMATYA

08/26/2022 08:47:17 PM

PALLAVI S MISHRA-KALYANI

08/30/2022 02:03:38 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MEMORANDUM

Date: July 29, 2021

From: Lili Pan, Yuzhuo Pan, and Sarah Dorff

Through: Jeanne Fourie Zirkelbach, Liang Li, and Robert Schuck

To: File for BLA 761139 S-21, Enhertu (fam-trastuzumab deruxtecan-nxki, T-DXd)

Re: Clinical Pharmacology Review

Daiichi Sankyo, Inc., submitted BLA 761139 S-21 for T-DXd for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy. T-DXd is a HER2-directed antibody and topoisomerase inhibitor conjugate. The clinical pharmacology review has been completed and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical pharmacology recommendation for this application is approval. Refer to the Multidisciplinary Review and Evaluation for additional details.

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/s/

LILI PAN
07/29/2022 07:57:49 AM

JEANNE FOURIE ZIRKELBACH
07/29/2022 09:09:05 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: July 29, 2022

To: Raniya Al-Matari, Regulatory Project Manager, Division of Oncology 2 (DO2)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

BLA: 761139/S-021

Background:

In response to DO2's consult request dated March 18, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 21 for ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use (Enhertu). This supplement provides for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.

OPDP's review on the proposed prescribing information are based on the draft labeling received by electronic mail from DO2 on July 26, 2022, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on July 29, 2022.

Thank you for your consult. If you have any questions, please contact Koung Lee at 240-402-8686 or Koung.lee@fda.hhs.gov.

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/

KOUNG U LEE
07/29/2022 04:00:36 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 29, 2022

To: Raniya Al-Matari
Regulatory Project Manager
Division of Oncology 2 (DO2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, WOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Koung Lee, RPh, MSHS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ENHERTU (fam-trastuzumab deruxtecan-nxki)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761139

Supplement Number: S-021

Applicant: Daiichi Sankyo, Inc.

1 INTRODUCTION

On February 16, 2022, Daiichi Sankyo, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy for Biologics License Application (BLA) 761139/S-021 for ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. With this supplement, the Applicant is proposing an additional indication for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA approved test, and who have received a prior systemic therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on March 18, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENHERTU (fam-trastuzumab deruxtecan-nxki) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ENHERTU (fam-trastuzumab deruxtecan-nxki) injection MG received on February 16, 2022, and received by DMPP and OPDP on July 26, 2022.
- Draft ENHERTU (fam-trastuzumab deruxtecan-nxki) injection Prescribing Information (PI) received on February 16, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 26, 2022.
- Approved ENHERTU (fam-trastuzumab deruxtecan-nxki) injection labeling dated May 4, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
07/29/2022 10:14:37 AM

KOUNG U LEE
07/29/2022 11:19:07 AM

BARBARA A FULLER
07/29/2022 11:34:44 AM

LASHAWN M GRIFFITHS
07/29/2022 11:37:53 AM

LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 19, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761139/S-021
Product Name, Dosage Form, and Strength:	Enhertu (fam-trastuzumab deruxtecan-nxki) for Injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Daiichi Sankyo, Inc
FDA Received Date:	May 18, 2022
OSE RCM #:	2022-571
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

Daiichi Sankyo, Inc submitted an Efficacy Supplement for Enhertu (fam-trastuzumab deruxtecan-nxki) for Injection to add the following indication:

Enhertu® is indicated for the treatment of adult patients with unresectable or metastatic nonsmall cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on [REDACTED] (b) (4) [REDACTED] and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Enhertu prescribing information and medication guide for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed changes to Section 2 Dosage and Administration of the Enhertu PI and determined that it is acceptable from a medication error perspective. We reviewed Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information and noted that there are no changes in these sections. We also

reviewed the proposed changes to the Medication Guide and determined that the proposed changes are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Enhertu PI and Medication Guide are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Enhertu received on February 16, 2022 from Daiichi Sankyo, Inc.

Table 2. Relevant Product Information for Enhertu	
Initial Approval Date	12/20/2019
Proper Name	fam-trastuzumab deruxtecan-nxki
Indication	Currently approved: - 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. - adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. Proposed addition: - adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy.
Route of Administration	intravenous
Dosage Form	for Injection
Strength	100 mg/vial
Dose and Frequency	Currently approved: - Breast cancer: 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. - Gastric cancer: 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Proposed addition: - Lung cancer: (b) (4) given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
How Supplied	Carton of one single-dose vial
Storage	Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution.
Container Closure	10 mL (b) (4) glass vial and sealed with a (b) (4) rubber stopper, and a (b) (4) aluminum yellow flip-off crimp cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 27, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Enhertu since November 19, 2021. Our search identified 2 previous reviews^{a,b}, and we confirmed that our previous recommendations were implemented.

^a Gao, T. Label and Labeling Review for Enhertu (BLA 761139/S-017 and S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Mar 3. RCM No.: 2021-2123.

^b Gao, T. Memorandum Review of Revised Label and Labeling Review for Enhertu (BLA 761139/S-017 and S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Mar 29. RCM No.: 2021-2123-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Enhertu labels and labeling submitted by Daiichi Sankyo, Inc.

- Prescribing Information (Image not shown) received on May 18, 2022, available from <\\CDSESUB1\evsprod\bla761139\0215\m1\us\114-labeling\draft\labeling\us-pi-tracked.docx>
- Medication Guide received on May 18, 2022, available from <\\CDSESUB1\evsprod\bla761139\0215\m1\us\114-labeling\draft\labeling\us-medguide-tracked.docx>

G.2 Label and Labeling Images

N/A

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TINGTING N GAO
05/19/2022 10:55:35 AM

ASHLEIGH V LOWERY
05/19/2022 11:30:30 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761139Orig1s021

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 137009

MEETING MINUTES

Daiichi Sankyo, Inc.
Attention: David Rusnak, JD
Associate Director Regulatory Affairs Strategy
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Mr. Rusnak:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fam-trastuzumab deruxtecan-nxki.

We also refer to the teleconference between representatives of your firm and the FDA on September 10, 2021. The purpose of the meeting was to discuss the results of Study U204 in support of a supplemental New Drug Application.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Kwadwo Korsah, Pharm.D., M.S.
Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic
Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹ 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>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sBLA

Meeting Date and Time: September 10, 2021; 3:00 – 4:00pm, EST.
Meeting Location: Teleconference

Application Number: IND 137009
Product Name: Fam-trastuzumab deruxtecan-nxki

Indication: Treatment of patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy

Sponsor Name: Daiichi Sankyo, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Paz Vellanki
Meeting Recorder: Kwadwo Korsah

FDA ATTENDEES

Harpreet Singh, MD, Director, DO2
Martha Donoghue, MD, Deputy Director, DO2
Erin Larkins, MD, Associate Director (acting), DO2
Nicole Drezner, MD, Clinical Team Leader
Paz Vellanki, MD, PhD., Clinical Team Leader (acting)
Bernardo Haddock Lobo Goulart, MD, Clinical Reviewer
Katie Chon, PharmD, Clinical Reviewer
Erica Nakajima, MD, Clinical Reviewer
Emily Wearne, PhD, Nonclinical Team Leader (acting)
Pallavi Mishra-Kalyani, PhD, Biometrics Team Leader
Xiaoxue Li, PhD, Biometrics Reviewer
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader
Suryatheja Ananthula, PhD, Clinical Pharmacology Reviewer
Youwei Bi, Clinical Pharmacology Reviewer
Jun Liu, PhD, Product Quality Reviewer
Kwadwo Korsah, PharmD, Regulatory Health Project Manager
Rama Kamesh Bikkavilli, Biologist, CDRH

SPONSOR ATTENDEES

Daiichi Sankyo

Gilles Gallant, BPharm, PhD, FOPQ Senior Vice President, Global Head Oncology Development, Oncology R&D

Javad Shahidi, MD, MSc Vice President, Global Team Leader, Oncology R&D

Gerold Meinhardt, MD Executive Director, Global Oncology R&D

Kapil Saxena, MD, MSc Senior Director, Global Oncology R&D

Kaline Pereira, MD, Senior Director, Global Oncology R&D

Eric Richards, MS, MPH, Senior Vice President, Head of Global Regulatory Affairs

Amita Chaudhari, MSc Executive Director, Global Regulatory Affairs, Oncology

Aaron Schetter, PhD, MPH, Senior Director, Companion Diagnostics Global Regulatory Affairs, Oncology

David Rusnak, JD, Associate Director, Global Regulatory Affairs, Oncology

Anne Tirouvanziam-Martin, Director, EU Regulatory Affairs, Oncology

Pranav Patel, BPharm, Manager, Global Regulatory Affairs, Oncology

Ryo Muto, Associate Director, Global Regulatory Affairs, Oncology

Qiang Wang, PhD, Senior Director, Biostatistics

Lin Zhang, MD, Vice President, Clinical Safety and Pharmacovigilance

Yingkai Cheng, MD, PhD Senior Director, Clinical Safety and Pharmacovigilance

Tushar Garimella, PhD, Senior Director Clinical Pharmacology, Quantitative Clinical Pharmacology

Amit Khatri, PhD Director, Quantitative Clinical Pharmacology

Patrik Vitazka, MD, PhD Senior Director, Companion Diagnostics

AstraZeneca

Suzanne Volpe, MS, RAC Senior Director Regulatory Affairs

Mark Lanasa, MD, PhD Vice President, Clinical Development

BACKGROUND

Regulatory

Fam-trastuzumab deruxtecan-nxki for injection, sold under the tradename Enhertu, is FDA approved for the treatment of adult patients with: HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting (approved dosage: 5.4 mg/kg as an intravenous infusion (IV) once every 3 weeks); and locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen (approved dosage: 6.4 mg/kg IV once every 3 weeks).

On January 22, 2020, a Type C meeting was held between FDA and Daiichi Sankyo, Inc. to discuss the potential for data from an activity-estimating clinical trial, Study DS8201-A-U204 (Study U204; DESTINY-Lung01), to support a marketing application under accelerated approval for T-DXd for (b) (4)

(b) (4). FDA stated results from 90 patients (b) (4) may be adequate to support an accelerated approval depending on the magnitude of overall response rate (ORR), durability of response and a favorable risk:benefit profile. FDA stated Daiichi should ensure a minimum follow-up of 6 months past onset of response for all responders in order to allow adequate assessment of durability. FDA also advised Daiichi to conduct head-to-head comparisons for safety profiles between the 6.4 mg/kg every 3 weeks (Q3W) vs 5.4 mg/kg Q3W dosage regimens for all patients with NSCLC and across tumor types.

On May 14, 2020, T-DXd was granted breakthrough therapy designation (BTD) for the treatment of patients with metastatic NSCLC whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy.

(b) (4)

On July 7, 2020, a Type B meeting was held between FDA and Daiichi Sankyo, Inc. to discuss Study U206 (DESTINY-Lung02), a randomized study of patients with HER2 mutant NSCLC to investigate two doses of T-DXd: 5.4 mg/kg Q3W compared to 6.4 mg/kg Q3W. Daiichi Sankyo indicated that the objectives of Study U206 were to: 1) (b) (4) and 2) assess the benefit-risk profile of T-DXd at 5.4 mg/kg for the treatment of HER2-mutant NSCLC.

(b) (4)

FDA also indicated that the proposed population of patients with refractory NSCLC is particularly vulnerable to pulmonary toxicity. FDA expressed concerns that there is evidence for a dose-dependent increase in pulmonary toxicity with increasing doses of T-DXd, and that the lower dose of T-DXd at 5.4 mg/kg has not yet been studied for HER2-mutant NSCLC. As Daiichi Sankyo had not appropriately explored the proper dose for patients for HER2-mutant NSCLC, an expected component of adequate drug development, FDA indicated that an Oncology Drugs Advisory Committee (ODAC) may be required if an application is submitted based on data from the DESTINY-Lung01 trial without additional data for patients with HER2 mutant NSCLC.

On May 28, 2021, a Type B End of Phase 2 (EOP2) meeting was held between FDA and AstraZeneca (b) (4)

(b) (4)

Nonclinical

Fam-trastuzumab deruxtecan-nxki (T-DXd) is a HER2-directed antibody-drug conjugate containing a topoisomerase I inhibitor (DXd) attached to the HER2 antibody by a cleavable linker. According to Daiichi Sankyo, T-DXd exhibits in vivo anti-tumor activity in patient-derived xenografts of HER2-mutated lung cancer. Daiichi Sankyo plans to submit pharmacology studies supporting the proposed HER2-mutated NSCLC indication in the supplemental BLA. Daiichi Sankyo plans to cross-reference BLA 761139 for previously reviewed nonclinical data.

Clinical Pharmacology

- In the dose expansion cohort of Study J101, 11 patients with HER2 mutations and 7 patients with HER2-overexpression were administered with T-DXd at a dose of 6.4 mg/kg every 3 weeks (Q3W). Study U204 was conducted in patients with HER2-overexpressing (T-DXd at 6.4 or 5.4 mg/kg, Q3W) and HER2-mutant (T-DXd at 6.4 mg/kg) NSCLC.
- Exposure parameters (C_{max} , AUC and C_{trough}) were compared among HER2-mutant NSCLC, HER2-overexpressing NSCLC, gastric cancer (GC), and breast cancer (BC). Data indicate that the exposure parameters among HER2-mutant NSCLC, HER2-overexpressing NSCLC, and GC are comparable. Simulated exposures for T-DXd and DXd for patients with HER2-mutant NSCLC dosed at 5.4 mg/kg T-DXd were comparable to exposures for patients with BC dosed at 5.4 mg/kg.
- Preliminary results suggest that a dose of 5.4 mg/kg Q3W T-DXd is expected to result in numerically lower incidence of any grade of interstitial lung disease (ILD), and lower incidence of adverse events (AEs) leading to dose reduction or dose discontinuation, compared to exposure expected following a dose of 6.4 mg/kg Q3W T-DXd.

Clinical

The sponsor intends to submit data from Study U204 (DESTINY-Lung01) supported by data from Study J101 as an application for approval of T-DXd at the 5.4 mg/kg Q3W dose for the treatment of patients with unresectable or metastatic NSCLC whose tumors have a HER2 (ERBB2) mutation, as detected by an FDA-approved test, and who have received a prior systemic therapy. Of note their data is derived from T-DXd at the 6.4 mg/kg Q3 dose in patients with lung cancer.

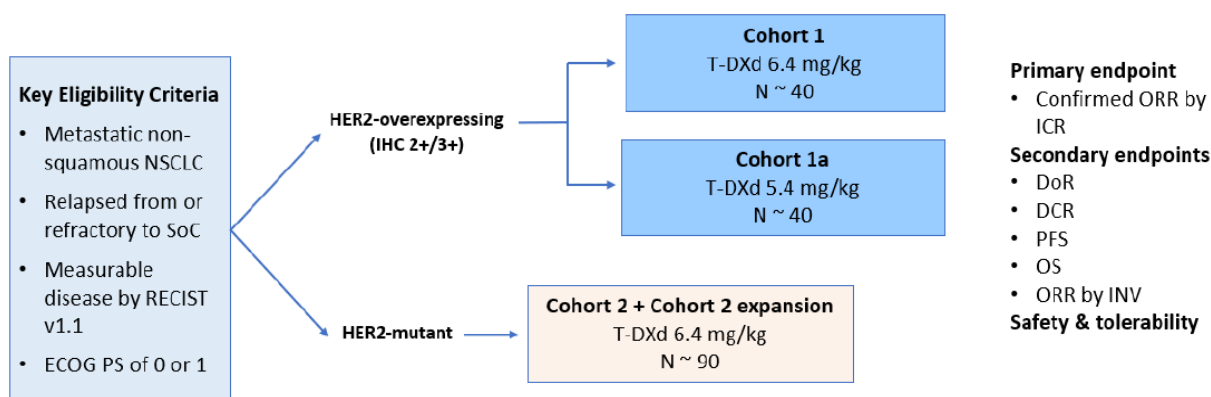
Study J101 – first-in-human trial of T-DXd in advanced solid tumors

Study J101 was a first-in-human, multicenter, dose escalation (N=27) and dose expansion (N=265) clinical trial of T-DXd in patients with advanced solid tumors including NSCLC. The dose expansion part of the study was intended to further assess the two recommended phase 2 doses (RP2Ds) of 5.4 mg/kg and 6.4 mg/kg in 5 cohorts of patients with breast cancer (Cohorts 2a, 2c, and 2e), gastric cancer (Cohort 2b), and solid tumors including NSCLC (Cohort 2d). Cohort 2d evaluated patients with HER2 overexpressing or HER2 mutant solid tumors (N=60) treated at 6.4 mg/kg.

Of the 18 patients with NSCLC who were enrolled into cohort 2d, 11 had HER2 mutant NSCLC and 7 had HER2 overexpressing NSCLC. Patients with HER2 mutant NSCLC had to have disease progression after prior standard of care therapy or have no standard therapies available. The overall response rate (ORR) in the HER2 mutant group (n=11) was 73% (95% CI: 39, 94) with a median duration of response (DoR) of 9.9 months (95% CI: 6.9, 11.5).

Study U204 – T-DXd for HER2-overexpressing and HER2-mutant NSCLC

Study U204 (Destiny-Lung01) was an international, open-label, multicenter, 2-cohort study to evaluate the safety and efficacy of T-DXd in patients with previously treated metastatic HER2- overexpressing non-squamous NSCLC (Cohort 1) or HER2-mutant non-squamous NSCLC (Cohort 2). The study schema is below.



Source: Meeting Package, p. 23

At the data cutoff (DCO) date of May 3, 2021, 91 patients with HER2 mutant NSCLC had enrolled and all had received the 6.4 mg/kg dose. The HER2 mutant patient cohort had a median age of 60 years, 66% were female, 25% were from Japan, 39% were from the U.S., and 36% were from Europe. Of the 91 patients, 95% had received prior platinum-based chemotherapy, 66% had received prior anti-PD-(L)1 therapy, and 63% had received prior platinum-based chemotherapy and anti-PD-(L)1 therapy either in combination or sequentially.

In the HER2 mutant cohort, the ORR by independent central review (ICR) was 55% (95% CI: 44%, 65%), with one complete response. The median DoR was 9.3 months (95% CI: 5.7, 14.7).

A summary of the primary efficacy results from Study U204, which support the proposed indication, are presented in the table below:

Primary Efficacy Results for Study U204, HER2-mutant NSCLC T-DXd at 6.4 mg/kg dose N=91	
Overall Response Rate	
ORR by ICR	55%
95% CI	44, 65
Median DoR, mos	9.3
95% CI	5.7, 14.7

Among the 91 patients with HER2 mutant NSCLC, the most common treatment emergent adverse events (TEAEs) (occurring in $\geq 30\%$) of any grade were nausea (76%), vomiting (46%), alopecia (46%), diarrhea (41%), constipation (37%), decreased appetite (35%), anemia (35%), fatigue (33%), and neutropenia (30%). Grade ≥ 3 TEAEs occurred in 69%, serious TEAEs occurred in 43%, and TEAEs associated with drug discontinuation occurred in 37%. TEAEs resulting in death occurred in 6 patients (7%) with one event each of pneumonitis, acute pulmonary edema, dyspnea, intestinal perforation, pneumocystis jirovecii pneumonia, and seizure. A total of 24 patients (26%) had drug-related ILD or pneumonitis as determined by an ILD adjudication committee, of which 6 patients (7%) had Grade ≥ 3 ILD or pneumonitis.

Ongoing Study U206 – randomized study of T-DXd 5.4 mg/kg vs 6.4 mg/kg for HER2 mutant NSCLC

Study U206 (DESTINY-Lung02) is an ongoing, global, multicenter, randomized study of 2 doses of T-DXd, 5.4 mg/kg Q3W vs 6.4 mg/kg Q3W, in patients with metastatic HER2-mutant NSCLC after at least one regimen of prior anticancer therapy that must have contained platinum-based chemotherapy. Approximately 150 patients from North

America, Europe, and Asia will be randomized in a 2:1 ratio to T-DXd 5.4 mg/kg (~ 100 patients) or T-DXd 6.4 mg/kg (~ 50 patients). The primary efficacy endpoint is ORR by ICR. The primary analysis will be performed after the last randomized patient has at least 9 months of treatment follow-up and a minimum of 6 months of follow-up for responders after onset of response. As of July 27, 2021, 28 patients have been randomized (19 patients at the 5.4 mg/kg dose and 9 patients at the 6.4 mg/kg dose). Enrollment is expected to be complete by September 2022. (b) (4)

[REDACTED]

The sponsor plans to submit an amendment for this protocol in the third quarter of 2021 to add a pre-specified interim analysis, that is planned to occur with a DCO date of December 2, 2021 with approximately 70 patients randomized by this time. The sponsor plans to submit results from this interim analysis as an amendment to the proposed sBLA by March 7, 2022, while the sBLA is under review. The results will include:

- A summary of the safety and PK at the first cycle from approximately 46 patients at the 5.4 mg/kg dose and 24 patients at the 6.4 mg/kg dose
- Efficacy results (ORR and DoR) from approximately 57 patients who have completed at least one post-baseline scan. Of these 57 patients, 24 patients at the 5.4 mg/kg dose and 11 patients at the 6.4 mg/kg dose will have completed at least two post-baseline scans.

(b) (4)

[REDACTED]

(b) (4)

[REDACTED]

Proposed Contents of the sBLA

- The proposed sBLA relies on the efficacy results from patients with HER2 mutant NSCLC (n=91) treated with T-DXd 6.4 mg/kg Q3W in Study U204 (DESTINY-Lung01) with supportive results from Study J101 Cohort 2d (n=11), an early-phase study in the same patient population treated at the same dose.
- Efficacy results from patients with HER2 mutant NSCLC treated with T-DXd 6.4 mg/kg Q3W from pivotal Study U204 and supportive Study J101 will be pooled in the summary of clinical efficacy (SCE) (total n=102).
- The sponsor proposes to use the totality of data from patients with HER2-overexpressing NSCLC (n=41 treated at the 5.4 mg dose and n=49 treated at the 6.4 mg/kg dose) and HER2-mutant NSCLC (n=102 treated at the 6.4 mg/kg dose), as well as data from patients across other tumor types to support the dosing recommendation for T-DXd of 5.4 mg/kg Q3W for the proposed indication.
- Study U204 will provide the primary safety data in patients with HER2-mutant NSCLC treated with 6.4 mg/kg T-DXd (n = 91) and will be presented alongside pooled safety analyses. Additional pooled safety analyses will include:
 - HER2-mutant NSCLC treated at T-DXd 6.4 mg/kg in Studies U204 and J101 (n=102)
 - HER2-mutant and HER2 overexpressing NSCLC treated at T-DXd 6.4 mg/kg in Studies U204 and J101 (n=158)
 - All tumor types treated at T-DXd 6.4 mg/kg in Studies J101, U204, U201 (breast cancer), J202 (gastric cancer), and U205 (n = approximately 619)

- o HER2 overexpressing NSCLC treated at T-DXd 5.4 mg/kg in Study U204 (n=41)
- o All tumor types treated at T-DXd 5.4 mg/kg in Studies J101, U204, and U201 (n = approximately 316)
- o All tumor types treated at T-DXd $\geq$ 5.4 mg/kg in Studies J101, U204, U201, J202, and U205 (n = approximately 962)

Each section of the summary of clinical safety (SCS) will discuss safety data from the NSCLC T-DXd 6.4 mg/kg Pool in relation to the NSCLC T-DXd 5.4 mg/kg Pool and to the All Tumor Types T-DXd 5.4 mg/kg Pool to provide a detailed assessment and comparison of safety for T-DXd in NSCLC across the 5.4 mg/kg and 6.4 mg/kg doses.

- The SCS will include analyses of adverse events (AEs), deaths, adverse events of special interest (AESIs), and laboratory evaluations. All corresponding tables and data listings supporting the SCS will be provided in Module 5.3.5.3 of the electronic Common Technical Document (eCTD).
- The integrated summary of safety (ISS) will include a link to the Clinical Study Report (CSR) for safety narratives. The sponsor proposes to submit safety narratives for patients with events that occurred after the first dose of study therapy to the end of the study follow-up period, defined per protocol as 40 (+7) days from the last administration of T-DXd. Narratives will also be provided for patients who have a serious adverse event (SAE) or adverse event of special interest (AESI) considered related to T-DXd by the investigator, in the post-study follow-up period. Narratives will be provided for deaths, SAEs, AEs associated with study drug discontinuation, laboratory data that meet Hy's criteria, AEs of ILD/pneumonitis, AEs of left ventricular dysfunction, and overdoses.
- Safety data in the post-marketing setting for patients with HER2-positive breast cancer dosed at 5.4 mg/kg and patients with HER2-positive gastric cancer dosed at 6.4 mg/kg through June 19, 2021 will be provided in Module 5.3.6 as links to previously submitted periodic safety reports (i.e., Periodic Benefit-Risk Evaluation Report [PBRER]).
- Datasets, SAS programs, and related documentation for Study J101 were previously submitted to the breast cancer BLA 761139 (SDN 0002) and the OSI package was previously submitted to the breast cancer BLA 761139 (SDN 0001). These items from Study J101 will be included by cross-reference in the planned sBLA.
- Benefit-risk assessment for both T-DXd 5.4 mg/kg and 6.4 mg/kg doses in patients with NSCLC (HER2-mutant and HER2 overexpressing) and other tumor types, including PK, safety, and efficacy data.

- Modeling and simulation data for T-DXd 5.4 mg/kg for HER2-mutant NSCLC
 - o Integrated population PK (PopPK) model for T-DXd and DXd incorporating data across the entire evaluated dose range in clinical studies (0.8 mg/kg to 8.0 mg/kg) and different tumor types (NSCLC, breast cancer, gastric cancer, and other tumors) to estimate PK exposure parameters for patients with HER2-mutant NSCLC at a 5.4 mg/kg dose.
 - o Exposure-response analyses for key endpoints to predict efficacy for T-DXd at 5.4 mg/kg and 6.4 mg/kg in patients with HER2-mutant NSCLC. The T-DXd and DXd exposures were simulated at the 5.4 mg/kg dose for HER2-mutant NSCLC using the PopPK model.
 - o Observed safety and exposure-response analyses for safety in HER2-mutant NSCLC to allow safety comparisons for T-DXd at the 5.4 mg/kg and 6.4 mg/kg doses in patients with NSCLC using the totality of data across the evaluated T-DXd dose range of 0.8 mg/kg to 8.0 mg/kg across different tumor types.
- Preliminary data from Study U206 will be summarized to provide available PK, safety, and efficacy data at the time of the proposed sBLA submission. Preliminary safety data from Study U206 will be available for approximately 28 patients (19 patients treated at the 5.4 mg/kg dose and 9 patients treated at the 6.4 mg/kg dose).
- If the sBLA is filed, the sponsor proposes to submit an amendment to the sBLA during the review, of interim analysis results from the ongoing U206 study after approximately 70 patients with HER2 mutant NSCLC have been enrolled. Of these patients, approximately 24 patients treated with T-DXd 5.4 mg/kg Q3W and 11 patients treated with T-DXd 6.4 mg/kg will be evaluable for a confirmed response.

A 90-day safety update will include an updated SCS and relevant datasets, with updated SAE listings from Studies U204 and U206. Post-marketing safety data will also be summarized. The sponsor proposes not to include additional safety data for Study J101 as only one patient remains on study treatment and 4 patients are in survival follow-up.

FDA sent Preliminary Comments to Daiichi on September 8, 2021.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Discussion during meeting: Daiichi Sankyo is internally discussing their plans regarding a submission of an sBLA based on data that are available now versus waiting until additional data are available regarding dose selection. Daiichi Sankyo has committed to sharing their plans with the FDA once they have determined their plans for sBLA submission.

1. Does the Agency agree that the results from the pivotal Study U204 (DESTINY-Lung01) with supportive results from Study J101 would support submission of a sBLA for the treatment of patients with unresectable or metastatic NSCLC whose tumors have a HER2 mutation and who have received a prior systemic therapy, for accelerated approval consideration?

FDA Response:

No. The available clinical data are not adequate to support submission of an sBLA for the proposed T-DXd dose of 5.4 mg/kg as all of the patients with HER2-mutant NSCLC received T-DXd at a dose of 6.4 mg/kg every 3 weeks (Q3W) in the U204 and J101 clinical trials. In the absence of clinical data indicating the optimal dose, consider postponing submission of the sBLA until data from the U206 trial informs the dose selection. Alternatively, if you choose to submit the sBLA prior to obtaining this data from the dose finding trial, we will assess whether the benefit-risk profile is acceptable for the 6.4 mg/kg dose. It is expected that your dose finding trial is well underway at the time of an sBLA submission.

2. Does the Agency agree with the proposed plan to use a modeling and simulation framework and data from Studies J101 and U204 (DESTINY-Lung01) along with available observed data from Study U206 (DESTINY-Lung02) to support the dosing recommendation for T-DXd for the proposed indication?

FDA Response:

No. See FDA response to Question 1. In the absence of clinical data supporting the dose selection, pharmacokinetics modeling and simulations alone are not adequate to support the dose recommendation of 5.4 mg/kg for the proposed indication.

3. Does the Agency agree with the proposal for the scope of CSR narratives and associated case report forms (CRFs) in the submission?

FDA Response:

Yes. However, see FDA response to Question 1.

4. Daiichi Sankyo plans to produce a Summary of Clinical Efficacy (SCE) and a Summary of Clinical Safety (SCS) in the sBLA in Module 2. These summary reports are equivalent to a fully Integrated Summary of Efficacy (ISE) and a fully Integrated Summary of Safety (ISS) but are written in the format of an SCE and SCS. The SCE and SCS content are expanded to add all items required in the ISE and ISS, as described in the CFR, the 1988 FDA Guidance (Guideline for the Format and Content of the Clinical and Statistical Sections of an Application 1988), and the 2009 FDA guidance (Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, Procedural 2009).

This approach was used to support the BLA 761139 marketing applications for BC and GC. Given the size of the proposed sBLA data package, it is the Sponsor's opinion that the text portions of the ISE and ISS can be appropriately described within the Module 2 summaries. The statistical outputs (tables, figures, and listings [TFLs]) and datasets will be provided in Module 5.3.5.3.

- (a) Does the Agency agree with the proposed content and format of the SCE (Module 2.7.3)?

FDA Response:

Yes. However, see FDA response to Question 1.

- (b) Does the Agency agree with the proposed content and format of the SCS (Module 2.7.4)?

FDA Response:

Yes. However, see FDA response to Question 1.

5. Does the Agency agree with the Sponsor's proposal for Study Data Tabulation Model (SDTM) and Analysis Data Model (AdaM) datasets in the electronic submission data plan?

FDA Response:

Overall, your proposal is acceptable. However, the datasets, SAS programs, and related documentation for Study J101, and the OSI package should be submitted

under this planned sBLA application rather than just cross-referenced to your prior application for breast cancer submitted to BLA 7611139.

6. Does the Agency agree with the content and timing of the proposed Safety Update?

FDA Response:

See FDA response to Question 1. We recommend that you consider postponing submission of the sBLA until data from the U206 trial informs the dose selection. However, if you choose to submit an sBLA prior to obtaining this data, the content and timing of the proposed safety update appear reasonable. Whether the benefit-risk profile is acceptable based on data from the proposed sBLA submission and the 90-day Safety Update will be a review issue.

7. Does the Agency agree with the proposal to provide interim analysis results from ongoing Study U206 during the sBLA review?

FDA Response:

See FDA response to Question 1. If you choose to submit an sBLA prior to obtaining clinical data to support the optimal dose of T-DXd, your proposal to provide interim analysis results, including efficacy, safety, and PK data, from the ongoing Study U206 during the sBLA review appears reasonable.

8. Does the Agency agree with the proposed assessments to support the clinical pharmacology package for the sBLA for the treatment of patients with unresectable or metastatic HER2-mutant NSCLC?

FDA Response:

See FDA response to Question 1. PK data can only be supportive of adequate clinical and safety data at the dosage proposed for approval.

9. Does the Agency agree that (b) (4)

[REDACTED]

FDA Response:

No. (b) (4)

[REDACTED]



10. Does the Agency agree that the proposed comprehensive table of contents for the sBLA with regards to Modules 1, 2, 4, and 5 will constitute a complete application for filing?

FDA Response:

Overall, the proposed table of contents is acceptable. However, see FDA responses to Questions 1 and 5.

11. Does the Agency agree with the content of the Financial Disclosure package?

FDA Response:

Yes. However, see FDA response to Question 1.

12. The Sponsor plans to participate in the Assessment Aid (AAid) program and proposes to submit the AAid at the time of the sBLA submission. Does the Agency agree?

FDA Response:

Yes. However, see FDA response to Question 1.

13. Daiichi Sankyo as the Sponsor of the sBLA has partnered with Thermo Fisher Scientific (TFS) for the development of a companion diagnostic to detect HER2 mutations in subjects with NSCLC. Thermo Fisher Scientific plans to submit a supplementary premarket approval for the Oncomine Dx Target Test as a companion diagnostic for T-DXd in HER2-mutant NSCLC contemporaneously with the sBLA submission. Does the Agency agree?

FDA Response:

Your proposal to submit a supplementary premarket approval (sPMA) application to CDRH for seeking a companion diagnostic claim for the ODxT Test contemporaneously with the submission of sBLA for T-DXd approval in HER2-mutant NSCLC appears to be acceptable.

You noted that based on preliminary data, of the 91 patients enrolled in Cohort 2 of Study U204, there was no tumor specimen to test for 5 (5.5%) patients, tumor specimens failed to yield sufficient amount of DNA for 22 (24.2%) patients, and there was failed tumor sequencing for 12 (13.2%) patients. CDRH is concerned that with this low sample ascertainment rate (52/91, 57%), determination of clinical effectiveness for the claimed CDx indication in NSCLC will be challenging. Therefore, we strongly recommend that you include additional clinical trial samples (from the ongoing T-DXd studies) to provide a robust assessment of the concordance between enrolling assay(s) and the proposed CDx to demonstrate clinical validation of the ODxT Test.

Please note that if efficacy results from any other study/cohort is used to support the approval of the drug, you should plan to re-test all the tumor samples from the additional patients (i.e., additional patients for the primary efficacy population in addition to the 91 patients from Study U204, Cohort 2) with ODxTT when assessing the clinical validation of the ODxTT.

CDRH will look into the totality of the data when reviewing the sPMA application.

ADDITIONAL COMMENTS

Additional Clinical Pharmacology Comments

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "[Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format](#)". Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

14. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
15. What are the exposure-response relationships for efficacy, safety and biomarkers?
16. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?

17. What is the impact of immunogenicity on exposure, efficacy and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

18. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate.
19. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
- Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.
20. Submit the following for the population pharmacokinetic analysis reports:
- Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.
- Refer to the [pharmacometric data and models submission guidelines](#).
21. Submit the following information and data to support the population pharmacokinetic analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
22. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans*:

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).³

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of "decentralize" aspects of clinical trials prospectively in the post-COVID era.

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

For details please refer to: <https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials>.”

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical*

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

*Specifications.*⁸

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁰

ISSUES REQUIRING FURTHER DISCUSSION

No issues.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments and handouts.

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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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