

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761394Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 6, 2024

To: Dana Kappel, Regulatory Project Manager, Division of Oncology I (DO1)

From: Courtney Leach, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for DATROWAY™ (datopotamab deruxtecan-xxxx) for injection, for intravenous use

BLA: 761394

Background:

In response to DO1's consult request dated February 2, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for DATROWAY™ (datopotamab deruxtecan-xxxx) for injection, for intravenous use.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 25, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on December 4, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on December 4, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Courtney Leach at (301) 796-1044 or Courtney.Leach@fda.hhs.gov.

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/s/

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**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: December 4, 2024

To: Dana Kappel, MA, MSc
Regulatory Project Manager
Division of Oncology I (DO1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Helen Young, MSN, MPH, CRRN, PHN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Courtney Leach, PharmD, BCCCP, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): DATROWAY (datopotamab deruxtecan-dlnk)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761394

Applicant: Daiichi Sankyo, Inc.

1 INTRODUCTION

On January 29, 2024, Daiichi Sankyo, Inc. submitted for the Agency's review an original Biologics Application (BLA) 761394 for DATROWAY (datopotamab deruxtecan-dlnk) for injection. The proposed indication for DATROWAY (datopotamab deruxtecan-dlnk) is for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior [REDACTED] (b) (4) for unresectable or metastatic disease.

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 I (DO1) on February 2, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DATROWAY (datopotamab deruxtecan-dlnk) for injection.

2 MATERIAL REVIEWED

- Draft DATROWAY (datopotamab deruxtecan-dlnk) for injection MG received on January 29, 2024, and received by DMPP and OPDP on November 25, 2024.
- Draft DATROWAY (datopotamab deruxtecan-dlnk) for injection Prescribing Information (PI) received on January 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 25, 2024.
- Approved ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection comparator labeling dated April 5, 2024.

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 APFont 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 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)

- ensured that the MG is consistent with the approved comparator labeling where applicable

4 DISCUSSION

DMPP maintained the order of the Warnings and Precautions in the “**What is the most important information I should know about DATROWAY?**” section, as directed by DO1, and to ensure consistency with the approved comparator, ENHERTU.

5 CONCLUSIONS

The MG is acceptable with our recommended changes.

6 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/

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Clinical Inspection Summary (CIS)

Date	10/17/2024
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Melanie Royce, M.D., Medical Officer Mirat Shah, M.D., Team Leader Laleh Amiri-Kordestani, M.D., Division Director Dana Kappel, Regulatory Project Manager Division of Oncology 1, Office of Oncology Drugs
NDA / BLA	BLA 761394
Applicant	Daiichi Sankyo, Inc.
Drug	Datopotamab Deruxtecan (Datroway®)
NME or Original NDA	Yes
Proposed Indication	Treatment of hormone receptor-positive, HER2-negative breast cancer (b) (4) for unresectable or metastatic disease
Consult Date	3/25/2024
CIS Goal Date	10/18/2024
Review Clock	Standard review
Action Goal Date	11/29/2024
PDUFA Due Date	1/29/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators (CIs) and a contract research organization (CRO) were inspected for Study D9268C00001 in support of this original BLA review: (1) Dr. Komal Jhaveri (New York, NY); (2) Dr. Seock-Ah Im (Seoul, South Korea); (3) Dr. Sonia Pernas Simon (Llobregat, Spain); and the imaging CRO [REDACTED] (b) (4)

For Drs. Jhaveri, Pernas Simon and the imaging CRO, the study appears to have been conducted in compliance with good clinical practice (GCP) principles and regulations. For Dr. Im, 9 non-serious adverse events (AEs) in 6 subjects were not reported: leg weakness and fall, forearm hematoma, lymphedema with left shoulder/back pain, vomiting, headache, nocturia, urticaria, swollen gums, and COVID-19 infection. OSI recommends the review division to consider these unreported AEs in the safety analysis. The AEs at the other two CI sites and the radiographic endpoint data for the co-primary efficacy analyses (progression-free and overall survival) were verifiable.

Based on the inspectional findings, the data from the inspected CI/CRO sites appear to be acceptable in support of the proposed indication for using datopotamab deruxtecan (Datroway®) for the treatment of hormone receptor-positive, HER2-negative breast cancer [REDACTED] (b) (4) for unresectable or metastatic disease.

II. BACKGROUND

This original BLA from Daiichi Sankyo (and AstraZeneca) supports the marketing approval of datopotamab deruxtecan (Dato-DXd) for the treatment of adults with [REDACTED] (b) (4) metastatic breast cancer, positive for the estrogen-progesterone hormone receptors (HR+) and negative for the human epidermal growth factor 2 receptor (HER2-) [REDACTED] (b) (4)

Breast cancer is the most common cancer worldwide (12%, 2 million new cases in 2020) and a major (fifth leading) cause of cancer death. Most cases are localized at diagnosis and one-third progress to metastatic disease with a median overall survival (OS) of 3 years (25% 5-year survival).

- In delivering the current standard of care (SOC), three breast cancer types are recognized based on the presence or absence of HER2, ER, and PR cell surface receptors: (1) ER-positive, PR-positive, and HER2-negative; (2) negative for all three receptors; and (3) positive for all three receptors. ER and PR receptors are referred together as HR receptors.
- The HR+ HER2- type is by far the most common (> 70%), for which the initial treatment of choice for metastatic disease is endocrine therapy, given either alone or in combination with other targeted therapies, followed by single-agent chemotherapy (typically eribulin, capecitabine, gemcitabine, or vinorelbine) given sequentially (diminishing treatment response to each agent). The current SOC for metastatic HR+ HER2- breast cancer varies and remains per local preference. As might be expected, OS declines with the continued management of progressing disease (30/18 months with 1/2 chemotherapies, respectively).

Dato-DXd is an antibody-drug conjugate consisting of a monoclonal antibody covalently linked to a cytotoxic drug. The antibody datopotamab (recombinant humanized IgG-1) directs the conjugate to the cancer cell to deliver the drug deruxtecan for specific targeted cell killing. Dato-DXd was developed as an anticancer agent jointly by Daiichi Sankyo and AstraZeneca.

The proposed indication for using Dato-DXd in advanced breast cancer is supported by the pivotal Study D9268C00001, identified at BLA review for on-site audit at four GCP inspections: three CIs (one domestic, two foreign) and the imaging CRO, where serial radiograms were interpreted as blinded independent central review (BICR) of cancer treatment response. The following protocol outline of the pivotal study highlights the major study features examined for GCP adherence at these four pre-approval surveillance inspections.

Study D9268C00001: A Study of Dato-DXd Versus Investigator's Choice Chemotherapy in Inoperable or Metastatic Hormone Receptor-positive, HER2-negative Breast Cancer

This open-label (sponsor-blind) randomized clinical trial was conducted (under IND 155696) over 21 months (10/2021 – 7/2023) in 732 subjects randomized in 20 countries at 166 CI sites: China (20 sites), Japan (19), United States (US, 14), Spain (11), United Kingdom (UK, 11), Italy (10), Brazil (9), France (8), India (8), Poland (8), Taiwan (8), South Korea (7), Argentina (6), Canada (5), Germany (5), South Africa (5), Hungary (4), Belgium (3), Netherlands (3), and Russia (2).

The primary study objective was to demonstrate the superiority of Dato-DXd therapy relative to investigator's choice of chemotherapy (ICC) in prolonging progression free survival (PFS) and OS in subjects previously treated with one or two lines of chemotherapy for inoperable/metastatic HR-positive, HER2-negative breast cancer. The CI chose one SOC agent as ICC.

Subject Selection

- Adults $\geq$ 18 years of age with unresectable (metastatic) HR+ HER2- breast cancer, status post prior chemotherapy for inoperable disease, and having at least one measurable lesion previously not irradiated (meeting target lesion criteria).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0/1 with no deterioration over last 14 days; adequate organ function (cardiac, lung, liver, kidney, bone marrow) within 7 days; for women, negligible pregnancy risk
- Eligible to receive Dato-DXd (no hypersensitivity or prior exposure) and at least one of: capecitabine, eribulin, gemcitabine, or vinorelbine
- Balanced subject proportions: for one versus two lines of prior chemotherapy, and for receipt versus no receipt of prior CDK4/6 inhibitor therapy
- Available tumor block, formalin fixed paraffin embedded (FFPE)
- HER2- defined as: immunohistochemistry (IHC) 0 or 1+
- IHC 2+ accepted as HER2- if negative for in-situ hybridization (ISH)

Exclusion: Potential subjects (meeting ALL criteria above) were excluded for ANY of:

- Radiotherapy for CNS lesions within two weeks, or any unresolved radiotherapy toxicity; inadequate washout/recovery period for any major prior therapy, including surgery; current use of oral estrogen for birth control
- Bone-only breast cancer metastases, or another primary malignancy (not considered cured)
- Any inadequately controlled or suspected infection (including serology for viral infections)
- Any condition that may complicate the study (CI judgment)

Randomization and Treatment Regimens

Subjects were randomized 1/1 to: (1) Dato-DXd intravenous, 6 mg/kg on Day 1 of 21-day cycles; or (2) ICC, one of the following agents (CI-chosen, considered SOC), 21-day cycles:

- Capecitabine: 1000 or 1250 mg/m² twice daily orally, Days 1-14
- Eribulin mesylate: 1.4 mg/m² IV, Days 1 and 8
- Gemcitabine: 1000 mg/m² IV, Days 1 and 8
- Vinorelbine: 25 mg/m² IV, Day 1 and 8

Randomization was stratified by prognostic variables: (1) numbers of prior chemotherapy lines (one or two); (2) geographic region (US, Canada, Europe versus Rest of World); and (3) prior targeted therapy in conjunction with chemotherapy using cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor (yes or no).

All subjects received the study therapy as randomized until CI recognition of: (1) disease progression (by radiography) according to *Response Evaluation Criteria in Solid Tumors* version 1.1 (RECIST), (2) unacceptable toxicity, or (3) any other reason to discontinue therapy.

Major Study Evaluations and Endpoints

Tumor treatment response was evaluated primarily and consistently by computed tomography (CT) or magnetic resonance imaging (MRI) of the head, chest, abdomen, and pelvis at screening (baseline) and at regular intervals during the study (every 3 months).

Bone scans (scintigraphy), skeletal survey (X-ray plain films), and/or positron emission tomography (PET) were additionally used as applicable to (more) accurately and comprehensively evaluate treatment response, including to resolve any CI versus BICR discrepancies in CT/MRI evaluations.

Co-Primary Efficacy Endpoints: Digital images were obtained/maintained at CI sites and sent electronically to the imaging CRO for BICR (per *Independent Review Charter*). All treatment decisions were based on CI imaging, independent of BICR.

- PFS (radiographic endpoint): time from randomization to disease progression per BICR
- OS (clinical endpoint): time from randomization to death from any cause

III. INSPECTION RESULTS

1. Komal Jhaveri, M.D.

Memorial Sloan Kettering Cancer Center
1275 York Ave
New York, NY 10065

Inspection Dates: 7/15 – 7/26, 2024

Protocol D9268C00001, Site 7804: 25 subjects were screened, 20 were enrolled, 1 remained on therapy, and 19 completed the study (7 died, therapy discontinued for 12). Four subjects were in active follow up after discontinuing therapy. The study audit included protocol adherence, institutional review board (IRB) oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 enrolled subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, protocol deviations (PDs), and use of non-study (concomitant) medications.

No significant GCP deficiencies or regulatory deviations were observed. The late reporting of two minor self-limited AEs (hives, back spasm) appeared unlikely to be significant. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

2. Sonia Pernas Simon, M.D.

Hospital Duran I Reynals
199 Edificio Principal
L`Hospitalet de Llobregat, Spain

Inspection Dates: 7/15 – 7/19, 2024

Protocol D9268C00001, Site 7002: 23 subjects were screened, 18 were enrolled, and all 18 completed the study (therapy discontinued). The study audit included protocol adherence, IRB oversight, staff training, and CI financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 enrolled subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study (concomitant) medications.

No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with GCP regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

3. Seock-Ah Im, M.D.

Seoul National University Hospital
101 Daehak-Ro, Jongno-Gu
Seoul, South Korea

Inspection Dates: 7/8 – 7/12, 2024

Protocol D9268C00001, Site 6001: 28 subjects were screened, 24 were enrolled, 2 remained on therapy, and 22 completed the study (therapy discontinued). The study audit included protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, and CI financial disclosure.

Subject case records were reviewed in detail for all enrolled subjects. The major study data were verified against source records for all enrolled subjects to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study (concomitant) medications.

The observed GCP deficiencies consisted of the following:

- Nine non-serious AEs in 6 subjects were not reported: leg weakness and fall, forearm hematoma, lymphedema with left shoulder/back pain, vomiting, headache, nocturia, urticaria, swollen gums, and COVID-19 infection.
- AEs of special interest (AESIs) were often not reported within 72 hours (of study visit, when AESI identified) as specified in the study protocol: late reporting by 7 days to 50 weeks for 26 events (oral mucositis, ocular keratitis, or infusion reactions) in 18 of the 24 enrolled subjects.
- Radiographic images were sent to the imaging CRO (uploaded, for BICR) routinely late (by 4 days up to 50 weeks), not within 48 hours as specified in the study protocol.

The major safety and efficacy data were otherwise verifiable.

Reviewer's comment: OSI recommends the review division to consider these unreported AEs in the safety analysis. The late reporting of AESIs or delayed uploading of radiographic images are not expected to have an impact on the study results (safety or efficacy).

4. [REDACTED] (b) (4)

[REDACTED] (b) (4)

Inspection Date: [REDACTED] (b) (4)

Protocol D9268C00001: This inspection was conducted in relation to (in follow up of) the findings at the last FDA inspection of this imaging CRO, with emphasis on the interim changes in general operating procedures and contracted responsibilities.

- The study-related records reviewed included contract documents, imaging review charters and related operating manuals, and reader qualification certification (selection and training).
- The data audit focused on the CI Sites 6001, 7002, and 7804 linked to this CRO inspection, to include image interpretation/adjudication of tumor lesions (locations, measurements) and changes from the previous evaluation.
- Subject-specific source data in *Tracking Platform* (imaging database and software) for target and non-target lesions (location, measurement, Sum of Lesion Diameter) were audited against the BLA data listings, to include time to event/PFS and visit responses per BICR/RECIST.

Two readers (radiologists) interpreted all images, and a third served as the adjudicator to reconcile any disagreement. *Tracking Platform* was certified to be compliant with electronic recordkeeping requirements specified in 21 CFR Part 11.

No significant GCP deficiencies were observed. Evidence of biased image interpretation (including unblinding) or other GCP deficiencies important to data quality was not observed. All images appeared to have been interpreted according to the applicable *Imaging Review Charter* and related manuals. All audited BLA data were verifiable against the source data in *Tracking Platform*.

{See appended electronic signature page}

John Lee, M.D., Primary Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DO1 / Division Director / Laleh Amiri-Kordestani
DO1 / Team Leader / Mirat Shah
DO1 / Clinical Reviewer / Melanie Royce
DO1 / Regulatory Project Manager / Dana Kappel

OSI / Office Director / David Burrow
OSI / Office Deputy Director / Laurie Muldowney
OSI / DCCE / Division Director / Kassa Ayalew
OSI / DCCE / GCPAB / Branch Chief / Jenn Sellers
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Clinical Analyst / John Lee
OSI / DCCE / GCPAB Program Analyst / Yolanda Patague
OSI / DCCE / GCPAB Program Analyst / Loreto-Corazon Lim

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/s/

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Medical Officer's Review of BLA 761-394
Ophthalmology Consultation

BLA 761-394

Submission date:	3/1/24
Consult Request:	3/1/24
Review date:	7/1/24
Desired date:	10/9/24

Sponsor: Daiichi Sankyo, Inc.

Drug Name: Datopotamab deruxtecan (Dato-DXd;DS-1062)

Indications: For the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior [REDACTED] (b) (4) for unresectable or metastatic disease.

Administration: The proposed dosing regimen is 6 mg/kg once every 21 days

Proposed Name: Datroway

Background:

This application is based on the results from the pivotal Phase 3 study D9268C00001 (TROPION-Breast01; TB01) in subjects with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy (TROPIONBreast01), with supportive evidence from the Phase 1 study DS1062-A-J101 (TROPION-PanTumor01; TP01) in subjects with breast cancer. There was a pre-BLA meeting held on 11/28/23.

Consult Request:

DO1 is reviewing a BLA for Dato-DXd, an NME antibody-drug conjugate intended for the treatment of HR-positive, HER2-negative unresectable/advanced breast cancer. Ocular surface toxicity is an important safety signal for this product and proposed for inclusion under Warnings in the USPI. We kindly request an Ophthalmology consultant to assist in the review of ocular toxicity data for this product and provide input on ocular toxicity labeling (Sections 2, 5, 6).

EDR Link to submission: [//CDSESUB1/evsprod/BLA761394/0001](https://CDSESUB1/evsprod/BLA761394/0001)

At a meeting with medical officer in July 2024 the overarching questions are:

1. The Sponsor conducted routine ophthalmologic exams in the pivotal trial. They are proposing [REDACTED] (b) (4) What is your assessment of that proposal?

2. Should routine, scheduled ophthalmologic monitoring be required in Sec 2 in labeling? (as was done in Tropion-Breast01 for breast cancer)?
3. The proposed dosage mods for Dato-DXd are based on CTCAE grading. For both of the products referenced below, we amended the dosage modification table in Section 2 to also incorporate exam findings. What are appropriate dosage modifications for ophthalmologic toxicity in Sec 2? Should these be guided by exam findings, and if so, how?
4.  (b) (4)

Reviewer's Comment:

This review only addresses areas of ophthalmologic concern.

Clinical Study:

TROPION-Breast01 (D9268C00001): A Phase 3, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or 2 Prior Lines of Systemic Chemotherapy

This is a Phase 3, open-label, randomized study of Dato-DXd vs. ICC (investigator's Choice Chemotherapy) in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who had been treated with one or 2 prior lines of systemic chemotherapy in the inoperable or metastatic setting. Approximately 700 patients were to be randomized in a 1:1 ratio to one of 2 intervention arms.

The study intervention arms were:

Arm 1: Dato-DXd (6 mg/kg IV on Day 1, Q3W)

Arm 2: ICC-

- Eribulin mesylate (1.4 mg/m² IV on Days 1 and 8, Q3W)
- Vinorelbine (25 mg/m² IV on Days 1 and 8, Q3W)
- Capecitabine (1000 or 1250 mg/m² oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice
- Gemcitabine (1000 mg/m² IV on Day 1 and Day 8, Q3W)

Table 3 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) ^a	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Informed consent: main study ^b	X									Section 5.1 and Appendix A.3
Informed consent: genetic sample and analysis (optional)	X									Section 5.1 and Appendix A.3
Study Procedures and Assessments										
Inclusion and exclusion criteria	X									Sections 5.1 & 5.2
Randomization		X ^c								Section 6.3
Demography	X									Section 5.1
Full physical examination (including weight and height)	X									Section 8.2.1
Targeted physical examination (including weight)		X ^d		X ^{e,f}		X	X			Section 8.2.1
Medical history ^g	X									Sections 5.1 & 5.2
Past and current medical conditions and prior anticancer therapy use	X									Sections 5.1 & 5.2
ECOG performance status	X	X ^d		X ^f		X	X			Section 8.2.5.4
12-lead ECG ^h	X	As clinically indicated				X				Section 8.2.3
Echocardiogram or MUGA (LVEF) ⁱ	X	As clinically indicated								Section 8.2.5.1
Vital signs including SpO ₂ ^j	X	X		X ^e		X	X			Section 8.2.2
Pulmonary function tests ^k	X	If ILD/pneumonitis is suspected								Section 8.2.5.2
ILD/pneumonitis investigation, including HRCT		If ILD/pneumonitis is suspected								Section 8.2.5.3

Table 3 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) ^a	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Ophthalmologic assessments ¹	X	<-----every 3 cycles from C1D1 onwards (eg. C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled Cycle Day 1 visit (but not after the scheduled visit) and as clinically indicated----->				X				Section 8.2.5.5
Oral care plan ^m	X	<----->								Section 8.2.5.6
AE ^{n,o}	X	<----->				X	X			Section 8.3
Prior and concomitant medication ^o	X	<----->				X	X			Section 6.5
Subsequent anticancer therapy							X		X	
Clinical Safety Laboratory Assessments										
Serum/urine pregnancy test (WOCBP only) ^p	X	X		X		X	X			Sections 5.1, 5.2 & 8.2.4
Hepatitis B and C serology ^q	X									Sections 5.2 & 8.2.4
HIV antibody test (as required by local regulations or IRB/IEC) ^{q,r}	X									Sections 5.2 & 8.2.4
Clinical safety laboratory assessments (clinical chemistry and hematology)	X	X ^d		X ^{d,e}		X	X			Section 8.2.4
Urinalysis	X	As clinically indicated								Section 8.2.4
Pharmacokinetics Assessments (for patients randomized to Dato-DXd only)										
PK blood sampling (before infusion) ^s		X		X (C2, C4, C6, C8, and C12, then every 4 cycles)		X				Section 8.5.1

Table 3 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix	
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) ^a	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit		
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)						
PK blood sampling (end of infusion) ^t		X ^u		X (C2, C4, C6, C8)						Section 8.5.1	
Immunogenicity Assessments (for patients randomized to Dato-DXd only)											
Blood sample for immunogenicity testing (ADA)		X ^s		X ^s (C2, C4, C6, C8, and C12; then every 4 cycles)		X	X				Section 8.5.2
Biomarker Assessments											
Mandatory tumor sample available (FFPE)	X										Section 8.6.1
Optional tumor biopsy (FFPE/FF) at progression ^v								X			Section 8.6.2
Optional paired tumor biopsy (FFPE/FF) ^v	X			X (C2D1 to C2D7 only)							Section 8.6.2
Optional bronchoalveolar lavage and lung biopsy sample on suspected ILD/diagnosis of ILD (added in CSP amendment 3)		As clinically indicated									Section 8.6.2
Plasma samples for biomarker analysis ^v	X	X		X (C2, C4)		X		X			Section 8.6.1
Serum samples for biomarker analysis ^v	X	X		X (C2, C4)		X		X			Section 8.6.1

Table 3 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix	
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) ^a	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit		
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)						
Plasma samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated									Section 8.6.1
Serum samples for biomarker analysis on suspected ILD/diagnosis of ILD		As clinically indicated									Section 8.6.1
Whole blood sample for gene expression analysis (RNA) ^y	X	X		X (C2, C4)				X			Section 8.6.1
Whole blood sample for gene expression analysis (DNA) ^y	X	X		X (C2, C4)				X			Section 8.6.1
Plasma samples for ctDNA analysis ^v	X	X		X (C2-C6, then Q6W)		X		X			Section 8.6.1
Genomics Initiative (optional)											
Optional exploratory genetic blood sample for Genomics Initiative ^{v,w}		X									Section 8.7 & Appendix D
Efficacy Assessments											
Tumor imaging (RECIST 1.1) ^x	X	Every 6 weeks (±7 days) from randomization for 48 weeks, then every 9 weeks (±7 days) thereafter until RECIST 1.1 disease progression (as assessed by the investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional FU scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later).									Section 8.1.1
Brain MRI/CT imaging ^y	X	Mandated for patients who had brain metastases documented at baseline, per RECIST 1.1 schedule.									Section 8.1.1
Whole body bone scan ^z	X	As clinically indicated									Section 8.1.1

Table 3 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) ^a	At PD	Survival FU (Every 3 months [±14 days] relative to the date of Safety FU Visit)	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Survival status								X	Section 7.1.3 & 8.1.4	
Time to second progression or death (PFS2)							X	X	Section 8.1.3	
Clinical Outcome Assessments										
ePRO training and setup		X								Section 8.1.5
EORTC QLQ-C30, EORTC IL 116, PGIS, EQ-5D-5L		C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT				At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD				Section 8.1.5
PRO-CTCAE, EORTC IL 117, PGI-TT		C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT				X				Section 8.1.5
PGIC		Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1)								Section 8.1.5
Medical Resource Utilization										
HOSPAD ^{aa}		X	X ^{bb}	X	X ^{bb}	X				Section 8.8
Study Intervention Administration										
Dato-DXd administration (IV)		X		X						Section 6
Capecitabine administration (oral)		Days 1 to 14 only, BID		Days 1 to 14 only, BID						Section 6
Eribulin administration (IV)		X	X	X	X					Section 6
Vinorelbine administration (IV)		X	X	X	X					Section 6
Gemcitabine administration (IV)		X	X	X	X					Section 6

^a The safety FU visit was to be performed 28 (+7) days after the last study intervention administration. If the date of discontinuation was over 35 days from last study intervention administration, then the EoT assessments could also function as the Safety FU visit.

^b Written informed consent and any locally required privacy act document authorization had to be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

^c Every effort was to be made to minimize the time between randomization and starting treatment (ie, no more than 3 days from the date of randomization).

^d If safety assessments were performed within 72 hours prior to starting Day 1 of a cycle, they did not have to be repeated, if the patient's condition had not changed.

^e For patients randomized to ICC, routine clinical care was to be performed in accordance with local practice.

^f Within 3 days prior to administration of study intervention.

^g Includes ocular history (since prior ocular events may predispose to or cause dry eye/keratitis), as well as history, type and frequency of tobacco use, e-cigarette use, vaping (including dates).

^h Triplicate ECGs were to be taken at screening and EoT. Triplicate ECGs were to be taken in close succession, while in a supine/semi-recumbent position. Single ECGs were to be taken during treatment as clinically indicated.

ⁱ The same test had to be used for the patient throughout the study. ECHO/MUGA not required at EoT unless clinically indicated.

^j Vital signs and SpO₂ were to be performed both before and after study intervention administration (where applicable), and as clinically indicated during treatment. Patients were to remain at the site for at least 1-hour post-infusion (where applicable) for close observation for IRRs.

^k Pulmonary function tests at a minimum were to include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %), DLCO will be performed (when feasible); however, for patients with prior severe and/or clinically significant pulmonary disorders, DLCO was a requirement.

^l Ophthalmologic assessments (by a licensed eye care provider) including visual acuity testing, fluorescein staining, intraocular pressure, slit lamp examination and funduscopy were to be performed at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1, etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit), in addition to as clinically indicated while on trial, and at EoT (see CSP Section 8.2.5.5 [Appendix 16.1.1] for additional information). Assessment schedule amended to every 3 cycles in CSP amendment 1.

^m A daily OCP was to be started before study drug initiation, and had to be maintained throughout the study until 28 days after last dose. An oral care kit was provided at study enrollment and monthly thereafter until the Safety FU visit, which included a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash. An oral care plan patient information guide was to be given to each randomized patient before study drug initiation. Initiation of dexamethasone oral solution was to be strongly considered (see CSP Section 8.2.5.6 [Appendix 16.1.1] for details). Oral care plan added in CSP amendment 1.

ⁿ Data collection could be conducted by phone if not tied to a visit.

^o All AEs occurring after the patient signed the ICF and up to 28 (+7) days after the last dose of study drug (ie, the safety FU period), whether observed by the investigator or reported by the patient, were to be recorded on the AE eCRF page (see CSP Section 8.3 [Appendix 16.1.1] for additional information).

^p Negative serum pregnancy test performed within 72 hours before study intervention at screening and repeat urine or serum pregnancy tests (per institutional guideline) performed within 72 hours before infusion of each cycle and at EoT and during safety FU. A positive urine pregnancy test result had to immediately be confirmed using a serum test.

^q Prior HIV serology (anti-HIV with or without HIV RNA, as appropriate), hepatitis B serology (HBsAg, anti-HBs, and anti-HBc with or without HBV DNA, as appropriate), and hepatitis C serology (anti-HCV antibody with or without HCV RNA, as appropriate) testing results could be used if performed within 120 days before enrollment. In this case, there was no need for a repeat test during the 28-day screening period.

^r Patients had to be tested for HIV if acceptable by local regulations or an IRB/IEC. If an HIV infection met the criteria outlined in CSP Section 5.2 (see Appendix 16.1.1), the patients' viral RNA load and CD4+ cell count were to be monitored per local SoC (eg, every 3 months).

^s To be performed within 8 hours prior to the start of Dato-DXd infusion, except for the EoT visit, during which samples could be collected anytime during this visit.

^t To be performed within 1 hour after the end of Dato-DXd infusion.

^u An additional PK sample was to be taken 5 hours (± 1 hour) from the start of Dato-DXd infusion on C1D1.

^v Not applicable to patients in mainland China.

- ^w The sample for genetic research was to be obtained at Day 1 pre-dose. If, for any reason, the sample was not drawn at Day 1, it could be taken at any visit until the last study visit. Only 1 sample was to be collected per patient for genetics during the study.
 - ^x The baseline tumor assessment had to be performed within 28 days before randomization and as close as possible to the start of treatment. The assessment was to include CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis. Any other areas of disease involvement were to be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual patients. The FU assessments were to include CT/MRI with IV contrast of the chest, abdomen and pelvis and any other area where disease was identified at baseline. The assessment had to continue until **1 visit (per original schedule) after radiographic disease progression** (as assessed by investigator), whether or not the patient was still on treatment. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline was to be used in the subsequent tumor assessments.
 - ^y Patients with brain metastases at baseline had to have the lesions recorded as part of the RECIST assessment and have a brain scan performed per the tumor imaging schedule until radiological progression per RECIST. For patients in whom CNS metastases were first discovered at the time of screening, the treating investigator was to consider delay of randomization and study intervention to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity could have been required).
 - ^z Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray were to be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA.
 - ^{aa} The site was to complete the "Hospital Admission (HOSPAD)" form at the site at every scheduled clinic visit up to and including the post-study treatment discontinuation FU visit. If the patient discontinued study treatment for reasons other than RECIST progression, the HOSPAD form administration was continued until progression was confirmed. Study mandated visits were not to be included as a hospital admission.
 - ^{bb} Only applicable to patients who were required to attend study visits on Day 8 of each cycle (ie, those randomized to receive ICC which are administered by IV infusion).
- Note: All assessments on treatment days were to be performed prior to study intervention administration, unless otherwise indicated. Following the DCO for the primary analysis, PK assessments were to be discontinued. Data collection following final study analysis until the end of the study is described in Section 8 of the CSP (see Appendix 16.1.1).

Ophthalmic Exclusion Criteria

None.

Ophthalmologic Data Review Committee

As required by a global health authority, an independent Ophthalmologic DRC was responsible for reviewing the ophthalmic assessment data collected in approximately the first 100 randomized patients at baseline, every third cycle, as clinically indicated. Further details are available in the Ophthalmologic DRC charter.

Table 45 Overview of Adverse Events by Category (Safety Analysis Set)

AE Category	Number (%) subjects ^a	
	Dato-DXd N = 360	ICC N = 351
Any AE	350 (97.2)	337 (96.0)
Any AE possibly related to treatment ^b	337 (93.6)	303 (86.3)
Any AE of CTCAE Grade 3 or higher	117 (32.5)	190 (54.1)
Any AE of CTCAE Grade 3 or higher, possibly related to treatment ^b	75 (20.8)	157 (44.7)
Any AE with outcome = death	0 ^c	3 (0.9)
Any AE with outcome = death, possibly related to treatment ^b	0	1 (0.3)
Any SAE (including events with outcome = death)	54 (15.0)	64 (18.2)
Any SAE (including events with outcome = death), possibly related to treatment ^b	21 (5.8)	32 (9.1)
Any SAE (including events with outcome = death) of CTCAE Grade 3 or higher	47 (13.1)	60 (17.1)
Any SAE (including events with outcome = death) of CTCAE Grade 3 or higher, possibly related to treatment ^b	17 (4.7)	31 (8.8)
Any SAE leading to discontinuation of IP	4 (1.1)	4 (1.1)
Any SAE leading to discontinuation of IP, possibly related to treatment ^b	3 (0.8)	4 (1.1)
Any AE leading to discontinuation of IP	11 (3.1)	10 (2.8)
Any AE leading to discontinuation of IP, possibly related to treatment ^b	9 (2.5)	9 (2.6)
Any AE leading to dose modification of IP ^d	137 (38.1)	183 (52.1)
Any AE leading to dose reduction of IP	83 (23.1)	113 (32.2)
Any AE leading to dose interruption of IP	78 (21.7)	120 (34.2)
AESI		
AESI-defined ILD/pneumonitis (as assessed by investigator)	17 (4.7)	2 (0.6)
Adjudicated ILD	10 (2.8)	1 (0.3)
Adjudicated drug related ILD	9 (2.5)	0
Infusion-related reaction	32 (8.9)	12 (3.4)
Oral mucositis/stomatitis	211 (58.6)	61 (17.4)
Mucosal inflammation other than oral mucositis/stomatitis	5 (1.4)	1 (0.3)
Ocular surface toxicity	175 (48.6)	81 (23.1)

^a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

^b As assessed by the investigator. Includes adverse events with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy. Subjects who have an AE leading to discontinuation of treatment post the DCO date, have been reset to the action taken at the DCO date using the dosing information. This affects 0 subjects in Dato-DXd treatment group and 0 subjects in ICC treatment group. Subjects who have a maximum CTC Grade 5 post the DCO, have been reset to unknown at the DCO date. This affects 0 subjects in Dato-DXd treatment group and 0 in ICC treatment group.

- ^c One patient had an event of pneumonitis and died (initially assessed as Grade 3 and death due to disease progression) that was subsequently assessed by the ILD Adjudication Committee as fatal drug related ILD (Table 14.3.6.2.2.IA1).
- ^d Dose modification = dose reduction or drug interruption

CTCAE version 5.0

Source: Table 14.3.2.1.IA1, Table 14.3.6.3.4.IA1 and Table 14.3.6.1.1.IA1

Table 58 Overview of AESI Ocular Surface Toxicity by Category (Safety Analysis Set)

AESI Category ^a	Number (%) Subjects	
	Dato-DXd N = 360	ICC N = 351
Any AESI of ocular surface toxicity	175 (48.6)	81 (23.1)
Grade 1	139 (38.6)	67 (19.1)
Grade 2	33 (9.2)	14 (4.0)
Grade 3	3 (0.8)	0
Grade 4	0	0
Grade 5	0	0
≥ Grade 3	3 (0.8)	0
Possibly related to study treatment ^b	144 (40.0)	41 (11.7)
SAE	1 (0.3)	0
Outcome		
Recovered/Resolved	49 (13.6)	20 (5.7)
Recovered/Resolved with sequelae	0	0
Recovering/Resolving	17 (4.7)	8 (2.3)
Not recovered/not resolved	109 (30.3)	53 (15.1)
Fatal	0	0
Action taken ^c		
Dose not changed	155 (43.1)	75 (21.4)
Dose reduced	4 (1.1)	1 (0.3)
Dose interrupted	9 (2.5)	0
Dose withdrawn	1 (0.3)	0
Not applicable	7 (1.9)	5 (1.4)
Missing	0	0

- ^a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
- ^b As assessed by the investigator. Includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy. Subjects who have an AE leading to discontinuation of treatment post the data cut-off (DCO) date, have been reset to the action taken at the DCO date using the dosing information. This affects 0 subjects in Dato-DXd treatment group and 0 subjects in ICC treatment group. Subjects who have a maximum CTCAE Grade 5 post the DCO, have been reset to unknown at the DCO date. This affects 0 subjects in Dato-DXd treatment group and 0 in ICC treatment group.
- ^c Subjects with multiple events with different actions are counted more than once.

Reviewer’s Comment:

A higher proportion of patients had ocular surface toxicity AESIs in the Dato-DXd arm compared with the ICC arm (48.6% vs. 23.1%).

In both treatment arms, the majority of ocular surface toxicity AESI were CTCAE Grade 1 or Grade 2 (98.2% Data-DXd arm and 100% ICC arm). Events of CTCAE ≥ Grade 2 were reported for 10.0% patients in the Dato-DXd arm and 4.0% in the ICC arm.

In the Dato-DXd arm, 3 patients had a Grade 3 ocular surface toxicity AESIs (2 patients grade 3 dry eye one of which had concurrent grade 3 ulcerative keratitis and one patient with grade 3 punctate keratitis). One patient in the Dato-DXd arm had a serious ocular surface toxicity AESI. In the Dato-DXd arm, ocular surface toxicity AESIs were recovered/resolved in 13.6% of patients (5.7% in the ICC arm).

These events were not recovered/not resolved for 30.3% patients in the Dato-DXd arm and 15.1% patients in the ICC arm. In the Dato-DXd arm, 1 patient was withdrawn from study treatment due to dry eye.

Study TROPION-Breast01: Adverse Event of Special Interest by AESI Category (Safety Analysis Set)

	Dato-DXd N=360	ICC N=351
Ocular Surface Toxicity	175 (48.6%)	81 (23.1%)
Blepharitis	27	6
Conjunctivitis	15	3
Corneal disorder	2	1
Corneal erosion	1	1
Corneal infiltrates	1	0
Corneal lesion	1	0
Dry eye	87	46
Eye ulcer	1	0
FBS	1	0
Keratitis	30	9
Keratopathy	4	1
Lacrimation increased	26	3
Limbal stem cell deficiency	0	1
MGD	24	6
Ocular toxicity	1	0
Photophobia	3	0
Punctate keratitis	38	23
Superior limbic keratoconjunctivitis	1	0
Ulcerative keratitis	1	0
Vision blurred	13	3
Visual acuity reduced	1	1
Visual impairment	2	0
Xerophthalmia	5	1

From Table 14.3.6.1.2

Reviewer's Comment:

In the Dato-DXd arm most common AEs were dry eye (24.2%), keratitis and punctate keratitis (18.9%), blepharitis and meibomian gland dysfunction (14.2%), and lacrimation increased (7.2%). In the ICC arm the most common AEs were dry eye (13.1%) and keratitis and punctate keratitis (9.1%).

All of the above symptoms are consistent with the product causing dry eye symptoms (dry eye, keratitis and punctate keratitis, blepharitis and meibomian gland dysfunction, and lacrimation increased).

Study TROPION-Breast01: Time To Onset of First AESI (Days) (Safety Analysis Set)

	N	Mean	Standard Deviation	Min, Max
Ocular Surface Toxicity	175 (48.6%)	94.6	76.2	1, 442
Blepharitis	27	146.7	94.8	45, 400
Conjunctivitis	15	116.1	104.8	2, 339
Corneal disorder	2	159.5	54.5	121, 198
Corneal erosion	1	122.0	N/A	122, 122
Corneal infiltrates	1	121.0	N/A	121, 121
Corneal lesion	1	62.0	N/A	62, 62
Dry eye	87	95.1	74.6	65, 334
Eye ulcer	1	85.0	N/A	85, 85
FBS	1	66.0	N/A	66, 66
Keratitis	30	127.8	67.6	28, 315
Keratopathy	4	103.0	64.6	42, 184
Lacrimation increased	26	124.1	89.3	1, 309
MGD	24	155.3	91.4	5, 377
Ocular toxicity	1	42.0	N/A	42, 42
Photophobia	3	189.0	36.5	148, 218
Punctate keratitis	38	156.4	102.6	10, 442
Superior limbic keratoconjunctivitis	1	128.0	N/A	128, 128
Ulcerative keratitis	1	122.0	N/A	122, 122
Vision blurred	13	68.3	5	208
Visual acuity reduced	1	148.0	N/A	148, 148
Visual impairment	2	174.0	62.2	130, 218
Xerophthalmia	5	96.8	71	

From Table 14.3.6.1.9

Reviewer's Comment:

The median time to onset of ocular surface toxicity AESIs was shorter in the Dato-DXd arm compared with the ICC arm (65.0 days vs. 79.0 days).

Ophthalmological Assessments

There were more patients in the Dato-DXd arm (N = 244) compared with the ICC arm (N = 164) in the ophthalmologic analysis set. During treatment, patients receiving Dato-DXd were advised to use artificial tears and avoid contact lenses. The median number of times patients used

artificial tears was lower (2-3 times per day) than the recommended minimum of 4-8 times per day. This was consistent across the Dato-DXd and the ICC arms. During treatment, 2.9% to 5.9% in the Dato-DXd arm and 6.3% to 8.5% in the ICC arm of patients in both arms used contact lenses.

Study Code: D9268C00001 Phase III Page 1 of 1
 Unblinded IAI - Data Cut-off: 17JUL2023
 Table 14.3.8.6.19. IAI Eye-related concomitant medications, procedures and surgeries (Ophthalmologic analysis set)

Category Sub-category	Dato-DXd N=244 n (%)	ICC N=164 n (%)
Medications	152 (62.3)	68 (41.5)
Corticosteroids	11 (4.5)	3 (1.8)
Antibiotics	4 (1.6)	0
Other	151 (61.9)	68 (41.5)
Ocular procedures	3 (1.2)	0
Surgeries	1 (0.4)	0

Dose delays were permitted for Dato-DXd treatment and the dosing interval for the next Dato-DXd cycle could be shortened, as clinically feasible to gradually align with the schedule of tumor efficacy assessment. Two consecutive doses had to be administered at least 19 days apart.

Study intervention dose delay for conditions other than toxicity resolution were to be kept as short as possible. A dose could be delayed for up to 3 consecutive cycles from the planned date of administration. If a patient was assessed as requiring a dose delay longer than 3 consecutive cycles (ie. up to 84 days from last infusion date to the planned date of administration), the patient was to discontinue study intervention. All dose reductions and delays (including any missed doses), and the reasons for the reductions/delays were to be recorded in the eCRF.

Treatment cycles for a patient for whom Dato-DXd dosing was temporarily withheld for any reason could have future cycles scheduled based on the date of the last Dato-DXd dose. In the event of a dose interruption occurring prior to completion of PK/pharmacodynamic blood sampling in the study, investigators were to contact the study clinical lead for guidance regarding scheduling of these procedures.

In cases where a dose reduction was necessary, Dato-DXd was to be modified as follows: up to 2 dose reductions were permitted for patients receiving Dato-DXd. Once the dose of Dato-DXd had been reduced, no dose re-escalation was permitted. After the permitted dose reductions, if further toxicity meeting the requirement for dose reduction occurred, the patient was withdrawn from the study intervention. In a rare circumstance, one additional dose reduction was possible on a case-by-case basis only after discussion and agreement between the investigator and Sponsor.

Table 6 Dose Reduction Levels of Dato-DXd

Starting Dose (Dose Level 1)	Dose Level -1	Dose Level -2
6.0 mg/kg IV, Q3W	4.0 mg/kg IV, Q3W	3.0 mg/kg IV, Q3W

Investigators were to consider dose reductions or discontinuations of Dato-DXd according to the patient's condition and after discussion with the study clinical lead or designee.

Questions:

1. The Sponsor conducted routine ophthalmologic exams in the pivotal trial. (b) (4)
What is your assessment of that proposal?

No, we do not agree. We recommend performing routine ophthalmic exams as was performed in the clinical trial (Ophthalmologic assessments (by a licensed eye care provider) including visual acuity testing, fluorescein staining, intraocular pressure, slit lamp examination and fundoscopy will be performed at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit), in addition to as clinically indicated while on trial, and at end of treatment).

2. Should routine, scheduled ophthalmologic monitoring be required in Sec 2 in labeling? (as was done in Tropion-Breast01 for breast cancer)?

Yes.

3. The proposed dosage mods for Dato-DXd are based on CTCAE grading. For both of the products referenced below (Elahere and Tivdak), we amended the dosage modification table in Section 2 to also incorporate exam findings. What are appropriate dosage modifications for ophthalmologic toxicity in Sec 2? Should these be guided by exam findings, and if so, how?

We would recommend dosage modifications as in the Section 2 labeling as in Table 3 for the labeling of Elahere.

4. (b) (4)

We do not feel  ^{(b) (4)} is indicated for this product.

Sonal Wadhwa, MD
Medical Officer, Division of Ophthalmology

Rhea Lloyd, MD
Clinical Team Leader, Division
Ophthalmology

William Boyd, MD
Deputy Division Director, Division of
Ophthalmology

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/

SONAL D WADHWA
09/03/2024 10:20:59 AM

RHEA A LLOYD
09/04/2024 02:29:19 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: August 28, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Dana Kappel
DO1

Subject: QT Consult to BLA 761394 (SDN 0001)

Note: Any text in the review with a light background should be inferred as copied from the applicant's document.

This memo responds to your consult to us dated 6/17/2024 regarding the applicant's QT related statement in Section 12.2 of the label. We reviewed the following materials:

- Applicant's concentration QTc analysis report (BLA 761394 / SDN 001; [link](#));
- Previous IRT review(s) for [IND 155696 dated 02/01/2023](#) in DARRTS;
- Previous IRT review for trastuzumab deruxtecan (T-DXd) in [BLA761136 dated 10/30/2019](#) in DARRTS;
- Investigator's brochure (IND 136626/ SDN 1011; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (IND 155696 (17 January 2023) ([link](#))).

1 Responses for the Division

Consult Request: The review division is reviewing a BLA for Dato-DXd, an NME antibody-drug conjugate intended for the treatment of HR-positive, HER2-negative unresectable/advanced breast cancer. The review team is seeking CS-IRTs assistance in evaluating the QT-concentration analysis and verify the QT related information present in Section 12.3 of the label.

IRT's response for the Review Division:

Treatment with Dato-DXd did not cause large mean increase (i.e., ≥ 20 msec) in QT interval in subjects participating in study DS1062-A-J101. This study was a phase 1, 2-part, multicenter, open-label, multiple-dose, first-in-human study to characterize pharmacokinetics and antitumor activity of Dato-DXd in subjects with advanced solid tumors in Japan and USA.

The applicant conducted concentration-QT analysis of time-matched PK/ECGs from 195 subjects receiving single or multiple doses of Dato-DXd at dose levels ranging from 0.27 to 10.0 mg/kg (2203 observations with DXd). According to the applicant's analysis, the predicted mean (90% CI) Δ QTcF at the geometric mean Cmax of DXd (3.51 ng/mL following 8 mg/Kg Q3W) was -0.293 (-1.71, 1.12) msec. Similarly, the predicted mean (90% CI) Δ QTcF at the geometric mean Cmax of Dato-DXd (201 μ g/mL following 8 mg/Kg Q3W) was 0.858 (-0.468, 2.18) msec indicating that at the maximum recommended dose, Dato-Dxd treatment is not likely to cause $\geq$ 20 msec mean increase in QTc intervals.

The CS-IRT previously reviewed another DXd containing antibody-drug conjugate (ADC), fam-trastuzumab deruxtecan ([BLA761136 dated 10/30/2019](#)). Based on the QTc assessment of fam-trastuzumab deruxtecan, no large mean increases in QTc (i.e., $\geq$ 20 ms) were observed at a geometric mean Cmax of 12.3 ng/mL for deruxtecan.

In the current indication under BLA761394, the Cmax for DXd following treatment with the recommended therapeutic dose (6.0 mg/kg Q3W) of Dato-DXd is significantly lower compared to that of fam-trastuzumab deruxtecan (Cmax: 3.36 ng/mL vs. 12.3 ng/mL). This provides further support that treatment with Dato-DXd at the proposed therapeutic dose of 6.0 mg/kg Q3W is unlikely to result in large mean increases in QTc (i.e., $>$ 20 ms). Therefore, the CS-IRT did not conduct an independent analysis to verify the applicant's findings. The antibodies (trastuzumab and datopotamab) are composed of naturally occurring amino acids and therefore are not considered for the QTc assessment, as they have low likelihood of direct interactions with ion channels.

2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0001 from the CS-IRT. Our changes are highlighted ([addition](#), ~~deletion~~). This is a suggestion only and we defer the final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

 (b) (4)

 (b) (4) 1.7 times the recommended  (b) (4) dose, a mean increase in the QTc interval $>$ 20 ms was not observed.

Reviewer's comments: The labeling language was modified based on the draft guidance, "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" ([link](#)).

3 BACKGROUND

3.1 Product Information

Dato-DXd is an ADC that comprises recombinant humanized anti-TROP2 IgG1 monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug-linker, MAAA-1162a via thioether bonds. The released drug, MAAA-1181a, derivative of exatecan, inhibits DNA topoisomerase I and leads to apoptosis of the target tumor cells.

The applicant (Daiichi Sankyo and AstraZeneca) seeks approval of Dato-DXd for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)- positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior (b) (4) for unresectable or metastatic disease. The recommended maximum therapeutic dose of Dato-DXd for treatment of HR-positive/HER2-negative breast cancer is 6 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

3.2 Applicant's position related to the question

The applicant submitted results from concentration-QT analysis of data from study DS1062-A-J101 as a substitute for a dedicated QT study. The dataset contained 2205 ECG assessments with time matched Dato-DXd concentrations (2203 assessments with DXd) from 195 subjects with NSCLC in Dato-DXd dose levels ranging from 0.27 to 10.0 mg/kg. According to the applicant's analysis, the upper bound of the 90% CIs for ΔQTc at the geometric mean C_{max} for Dato-DXd and DXd at 8.0 mg/kg (the MTD) ranged from 1.12 to 2.59 ms and at 6.0 mg/kg, the corresponding 90% CIs for ΔQTc ranged from 1.11 to 1.99 ms. Also, the applicant mentions the results from dedicated QT study of ENHERTU (trastuzumab deruxtecan) which did not show large mean increases in QTc (i.e., >20 ms) at Dxd concentrations significantly higher than those observed with Dato-DXd at the recommended therapeutic dose.

Reviewer's Comment: The CS-IRT previously reviewed another ADC, fam-trastuzumab deruxtecan, which also uses deruxtecan as the payload ([BLA761136 dated 10/30/2019](#)). Based on the QTc assessment of fam-trastuzumab deruxtecan, no large mean increases in QTc (i.e., >20 ms) were observed at a geometric mean C_{max} of 12.3 ng/mL for deruxtecan. The PK parameters for deruxtecan (DXd or MAAA-1181a) following treatment with the therapeutic dose (6.0 mg/kg Q3W) of datopotamab deruxtecan (Dato-DXd) under a high clinical exposure scenario were significantly lower compared to fam-trastuzumab deruxtecan (C_{max} : 3.36 ng/mL vs. 12.3 ng/mL). This suggests that Dato-DXd at the proposed therapeutic dose of 6.0 mg/kg Q3W will not result in large mean increases in QTc (i.e., >20 ms). Therefore, CS-IRT has not conducted independent analysis to verify the applicant's findings. The antibodies (trastuzumab and datopotamab) are considered irrelevant for the QTc assessment because of low likelihood of their direct interactions with ion channels.

3.3 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety.

Table 1: Summary of dose and exposure assessment

Mean C_{max}

Highest therapeutic or clinical trial dosing regimen	6.0 mg/kg Q3W IV infusion	2.82 ng/mL ($C_{\max,ss}$) ^{1,2}
Applicant's High clinical exposure scenario	1.19-fold increase in subjects with high body weight (103 kg)	3.36 ng/mL
Highest dose in QT assessment	8.0 mg/kg Q3W IV infusion	3.51 ng/mL
$C_{\max}$ Ratio	~1	

¹Value of $C_{\max}$ presented was observed after the first cycle. As accumulation of Dxd was not observed with 6.0 mg/kg Q3W dosing regimen, the $C_{\max}$ value observed after first dose represents the steady state concentrations.

² $C_{\max}$ value is for Dxd

3.4 Nonclinical Cardiac Safety

Refer to the review dated [02/02/2023 under IND 155696](#) in DARRTS.

3.5 Clinical Cardiac Safety

Refer to the review dated [02/02/2023 under IND 155696](#) in DARRTS.

3.6 Summary results of prior QTc assessments

The IRT has previously reviewed another ADC with deruxtecan as the payload. The following is a summary from our review for trastuzumab deruxtecan (T-DXd) in [BLA761136 dated 10/30/2019](#) in DARRTS.

1 SUMMARY

No large mean increases in QTc (i.e., >20 ms) was observed in this QT assessment of ENHERTU.

The effect of ENHERTU (fam-trastuzumab deruxtecan) was evaluated in Study DS8201-A-J102. The highest dose evaluated was 6.4 mg/kg administered every 3 weeks, which covers the therapeutic exposures. The data were analyzed using by-timepoint analysis as the primary analysis, which did not suggest that ENHERTU is associated with large mean increases in the QTc interval (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), concentration-QTc analysis (section 4.5), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	Δ (ms)	90% CI (ms)
QTc	6.4 mg/kg every 3 weeks	Period 3 hour 7	5.0	(1.2, 8.7)

The observed geometric mean $C_{\max}$ of MAAA-1181a is 12.3 ng/mL in this study. It covers the maximum therapeutic exposure at the therapeutic dose (8.2 ng/mL, Table 3.4 in the Summary of Clinical Pharmacology Studies). At this time, none of the intrinsic or extrinsic factors being evaluated (i.e., age, sex, race, weight, mild hepatic impairment, mild and moderate renal impairment, and strong inhibition of OATP1B, P-gp, or CYP3A) are expected to result in higher than 30% increase in steady state $C_{\max}$ of MAAA-1181a.

Reviewer's Comments: The C_{max} values of MAAA-1181a (DXd) following treatment with trastuzumab deruxtecan (T-DXd) are higher than those following treatment with datopotamab deruxtecan (Dato-DXd) at comparable doses (i.e., 6.4 mg/kg Q3W vs. 6.0 mg/kg Q3W). This suggests that Dxd released from Dato-DXd will have relatively lower risk for QTc prolongation and adverse events compared to T-DXd.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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ELIFORD N KITABI
08/28/2024 06:31:20 PM

ANANTHA RAM NOOKALA
08/28/2024 06:40:57 PM

CHRISTINE E GARNETT
08/29/2024 08:45:25 AM

LABEL AND 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:	June 26, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2) Division of Oncology 1 (DO1)
Application Type and Number:	BLA (b) (4) (DO2) and BLA 761394 (DO1)
Product Name, Dosage Form, and Strength:	Datroway (datopotamab deruxtecan-xxxx) ^a For Injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Daiichi-Sankyo, Inc.
FDA Received Date:	December 20, 2023 and April 18, 2024 (BLA (b) (4)) January 29, 2024 and May 1, 2024 (BLA 761394)
TTT ID #:	2023-7554 (BLA (b) (4) /DO2) 2024-8096 (BLA (b) (4) /DO1)
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder datopotamab deruxtecan -xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for Datroway (datopotamab deruxtecan-xxxx) For Injection, the Division of Oncology 2 (DO2) and Division of Oncology 1 (DO1) requested that we review the proposed Datroway Prescribing Information (PI), Medication Guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA (b) (4) (DO2) and BLA 761394 (DO1).

Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Datroway Medication Guide (MG) and carton labeling and determined that they are acceptable from a medication error perspective.

However, the proposed Datroway Prescribing Information (PI) and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) and Division of Oncology 1 (DO1) in Section 4 and for Daiichi-Sankyo, Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2) AND DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Section 2 Dosage and Administration

- a. Revise the opening statements of Section 2.4 *Preparation and Administration* to provide important product information to support the safe handling of the product during preparation and administration as follows:

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

DATROWAY (datopotamab deruxtecan-xxxx) is a hazardous drug. Follow applicable special handling and disposal procedures.

- b. In the Reconstitution section, the stated maximum refrigerated storage time for reconstituted vials does not clearly indicate that the maximum

storage time from reconstitution to the end of administration should not exceed 24 hours. For improved clarity, revise the statement to read:

“If not used immediately, (b) (4)
(b) (4) at 2°C to 8°C (36°F to 46°F) for up to 24
hours, (b) (4)
(b) (4) Do not freeze.”

- c. In the Dilution section, the stated maximum room temperature and refrigerated storage time periods for diluted solution does not clearly indicate that the maximum storage time includes preparation and infusion time. For improved clarity, revise the statement to read:

“If not used immediately, store (b) (4) at room
temperature for up to 4 hours including preparation (b) (4)
(b) (4) or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to
24 hours (b) (4)
(b) (4) Do not freeze.”

- d. (b) (4)
(b) (4) We recommend removing (b) (4) (b) (4)
(b) (4) Revise
the established names for the diluents so that they are presented as
follows:

5% Dextrose Injection (b) (4)

- e. Revise the Administration section as follows to clarify information regarding the maximum storage time for DATROWAY infusions before they must be discarded and the proper handling of refrigerated infusions prior to administration:

Administration

- The maximum time from reconstitution of the vial through the end of administration should not exceed (b) (4) 24 hours (b) (4) Discard if storage time exceeds these limits.
- 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, protected from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
- Administer TRADENAME as an intravenous infusion only with an infusion line and tubing set made of polyvinyl chloride (PVC), polybutadiene or low-density polyethylene.
- Administer TRADENAME with a 0.2 micron in-line polytetrafluoroethylene, polyethersulfone or nylon 66 filter.
- Do NOT administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light during administration.
- Do not mix TRADENAME with other drugs or administer other drugs through the same intravenous line.

- First infusion: Administer infusion over 90 minutes. Observe patients during the infusion and for at least (b) (4) following the initial dose, for signs or symptoms of infusion-related reactions.
- (b) (4)

5 RECOMMENDATIONS FOR DAIICHI-SANKYO, INC.

A. General Comments (Container Label(s) & Carton Labeling)

1. We refer to the Proprietary Name Request Conditionally Acceptable letter dated March 14, 2024 for BLA (b) (4) that concluded the proposed proprietary name, Datroway, is conditionally acceptable. Replace all instances of the proprietary name placeholder "TRADENAME", with the conditionally acceptable name, "Datroway".

B. Container Label

1. To support the proper storage of Datroway vials, revise the storage statement to read "Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). Protect from light."

C. Carton Labeling

1. As currently presented, the reconstitution and the resulting concentration information is embedded as part of the "Contents" which may be overlooked. Separate and present the sentence "Following reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration of datopotamab deruxtecan-xxxx is 20 mg/mL." as a new paragraph so that the sentence reads:

Reconstitution: Following reconstitution with 5 mL of Sterile Water for Injection, the resulting concentration of datopotamab deruxtecan-xxxx is 20 mg/mL.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Datroway received on April 18, 2024 (BLA (b) (4)) and May 1, 2024 (BLA 761394) from Daiichi-Sankyo, Inc.

Table 2. Relevant Product Information for Datroway		
Application #	BLA (b) (4) (DO2)	BLA 761394 (DO1)
Initial Approval Date	N/A	N/A
Nonproprietary Name	datopotamab deruxtecan-xxxx	
Indication	(b) (4)	For the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior (b) (4) for unresectable or metastatic disease.
Dosage Form	For Injection	
Strength	100 mg/vial	
Route of Administration	Intravenous Infusion	
Dose and Frequency	Starting dose: 6 mg/kg/dose intravenously every 3 weeks 1 st Dose Reduction: 4 mg/kg/dose 2 nd Dose Reduction: 3 mg/kg/dose	
How Supplied	Carton containing one 100 mg single-dose vial	
Storage	Store 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	(b) (4) glass, (b) (4) vial, 20 mm (b) (4) stopper with a 20 mm blue, aluminum seal with (b) (4) flip-off cap	

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Datroway labels and labeling submitted by Daiichi-Sankyo, Inc..

- Prescribing Information
 - Received on April 18, 2024 for BLA (b) (4) available from [\\CDSESUB1\EVSPROD\bla \(b\) \(4\)\0010\m1\us\114-labeling\draft\labeling\us-pi-clean.docx](\\CDSESUB1\EVSPROD\bla (b) (4)\0010\m1\us\114-labeling\draft\labeling\us-pi-clean.docx)
 - Received on May 1, 2024 for BLA 761394, available from <\\CDSESUB1\EVSPROD\bla761394\0010\m1\us\nonannotated-draft-label-tb-01-word.docx>
- Medication Guide
 - Received on December 20, 2023 for BLA (b) (4), available from [\\CDSESUB1\EVSPROD\bla \(b\) \(4\)\0001\m1\us\114-labeling\draft\labeling\us-medguide-clean.docx](\\CDSESUB1\EVSPROD\bla (b) (4)\0001\m1\us\114-labeling\draft\labeling\us-medguide-clean.docx)
 - Received on January 29, 2024 for BLA 761394, available from <\\CDSESUB1\EVSPROD\bla761394\0001\m1\us\nonannotated-draft-medication-guide-tb01.docx>
- Container label(s) received on December 20, 2023 (BLA (b) (4)) and January 29, 2024 (BLA 761394)
- Carton labeling received on December 20, 2023 (BLA (b) (4)) and January 29, 2024 (BLA 761394)

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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JANINE A STEWART
06/26/2024 06:01:13 PM

TINGTING GAO
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