Report on the Deliberation Results

December 11, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Datroway for Intravenous Drip Infusion 100 mg
Non-proprietary Name	Datopotamab Deruxtecan (Genetical Recombination) (JAN*)
Applicant	Daiichi Sankyo Company, Ltd.
Date of Application	March 14, 2024

Results of Deliberation

In its meeting held on December 6, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 25, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Datroway for Intravenous Drip Infusion 100 mg
Non-proprietary Name	Datopotamab Deruxtecan (Genetical Recombination)
Applicant	Daiichi Sankyo Company, Ltd.
Date of Application	March 14, 2024
Dosage Form/Strength	Powder in vials to be reconstituted for injection, each containing 108 mg of datopotamab deruxtecan (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Datopotamab Deruxtecan is an antibody-drug-conjugate (molecular weight: ca. 152,000) consisting of deruxtecan ((3*RS*)-1-[(10*S*)-10-benzyl-1-{[(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1*H*,12*H*-benzo[*de*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-1-yl]amino}-1,6,9,12,15,18-hexaoxo-3-oxa-5,8,11,14,17-pentaazatricosan-23-yl]-2,5-dioxopyrrolidin-3-yl group ($C_{52}H_{57}FN_9O_{13}$; molecular weight: 1,035.06)), which is composed of camptothecin derivative and linker, attached to an average of four cysteine residues of a recombinant monoclonal antibody. The antibody moiety is an anti-cell surface glycoprotein Trop-2 monoclonal antibody, the complementarity-determining regions of which are derived from mouse antibody and other regions are derived from human IgG1 and produced in CHO cells. The protein moiety is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

Heavy (H) chain

QVQLVQSGAE VKKPGASVKV SCKASGYTFT TAGMQWVRQA PGQGLEWMGW
INTHSGVPKY AEDFKGRVTI SADTSTSTAY LQLSSLKSED TAVYYCARSG
FGSSYWYFDV WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG
K

Light (L) chain

DIQMTQSPSS LSASVGDRVT ITCKASQDVS TAVAWYQQKP GKAPKLLIYS
ASYRYTGVPS RFSGSGSGTD FTLTISSLQP EDFAVYYCQQ HYITPLTFGQ
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

Pyroglutamic acid (partial): H-chain Q1

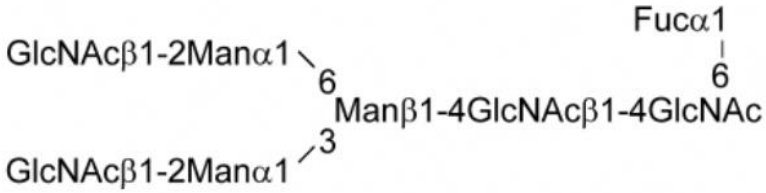
Potential drug binding sites: H-chain C224, H-chain C230, H-chain C233, L-chain C214

Glycosylation: H-chain N301

Partial processing: H-chain K451

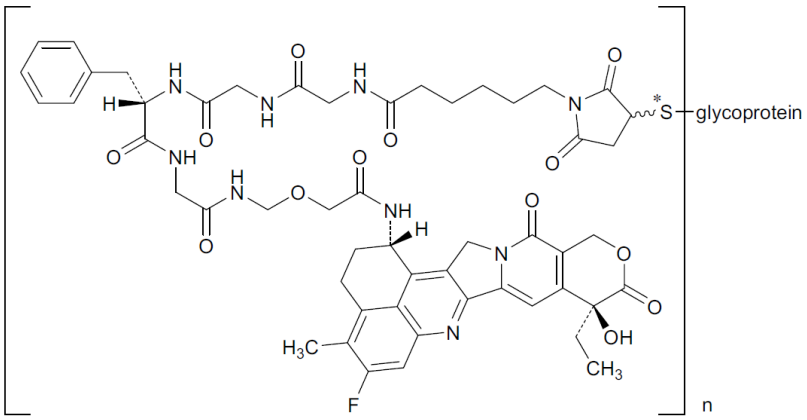
Disulfide bonds: H-chain C224–L-chain C214, H-chain C230–H-chain C230, H-chain C233–H-chain C233

Main proposed carbohydrate structure



GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Structural formula of deruxtecan site:



N = 4 (mean)

* A sulfur atom of a cysteine residue of the antibody moiety

Molecular formula: $C_{6464}H_{9984}N_{1708}O_{2016}S_{44}$ (protein moiety, four-stranded)

Molecular weight: approximately 152,000

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with unresectable or recurrent hormone receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative breast cancer who have received prior chemotherapy and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy

Dosage and Administration

The usual adult dosage is 6 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 2, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Datroway for Intravenous Infusion 100 mg
Non-proprietary Name	Datopotamab Deruxtecan (Genetical Recombination)
Applicant	Daiichi Sankyo Company, Ltd.
Date of Application	March 14, 2024
Dosage Form/Strength	Powder in vials to be reconstituted for injection, each containing 108 mg of datopotamab deruxtecan (genetical recombination)

Proposed Indication

Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy

Proposed Dosage and Administration

The usual adult dosage is 6.0 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Datopotamab deruxtecan is an antibody-drug conjugate (ADC) discovered by the applicant and comprises datopotamab (Dato), a trophoblast cell surface antigen (TROP)-2 directed immunoglobulin (Ig)G1 subclass humanized monoclonal antibody, which is linked to MAAA-1181a (DXd), a topoisomerase I-inhibiting camptothecin derivative, via a peptide linker.

Datopotamab deruxtecan binds to TROP-2 expressed on the cell membrane of tumor cells and undergoes internalization. After linker hydrolysis, released free DXd causes DNA damage, apoptotic cell death, and other effects, which are considered to suppress tumor growth.

1.2 Development history, etc.

Study TROPION-PanTumor01 (Study TP01) was a global phase I study conducted by the applicant from January 2018 in patients with unresectable or recurrent HR-negative, HER2-negative breast cancer. From October 2021, Study TROPION-Breast01 (Study TB01), a global phase III study, was conducted by the applicant and AstraZeneca in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who had previously received chemotherapy.

Applications were filed with the results from Study TB01 as a pivotal study in [redacted] 20[redacted] in the US and [redacted] 20[redacted] in Europe, and both applications are currently under review.

As of August 2024, datopotamab deruxtecan has not been approved in any country or region for the treatment of patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy.

In Japan, Studies TP01 and TB01 started enrolling patients from [redacted] 20[redacted] and [redacted] 20[redacted], respectively.

Recently, an application for marketing approval of datopotamab deruxtecan has been filed using results from Study TB01 as a pivotal study.

2. Quality and Outline of the Review Conducted by PMDA

Datopotamab deruxtecan is an ADC comprising Dato, a TROP-2 directed humanized monoclonal antibody that is bound to MAAA-1162a consisting of a camptothecin derivative (DXd) and a peptide linker.

2.1 Drug substance

[redacted] and [redacted] are controlled as critical intermediates of the drug substance.

2.1.1 Dato

2.1.1.1 Generation and control of cell substrate

Based on the amino acid sequence of a monoclonal antibody produced by immunizing [redacted] with [redacted], gene expression constructs for Dato were produced through genetic modification, etc. of humanized IgG1 antibody. These expression constructs were transfected into CHO cells. From the obtained cells, a clone most suitable for the manufacture of Dato was selected and used to prepare the master cell bank (MCB) and working cell bank (WCB).

Characterization and purity testing were conducted for the MCB, WCB, and cells cultured up to the limit of in vitro cell age (LIVCA) in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines Q5A (R1), Q5B, and Q5D. The results of the characterization and purity testing demonstrated genetic stability during production. Within the range tested, no viral or non-viral adventitious agents were detected other than general endogenous retrovirus-like particles from the rodent-derived cell lines.

Both the MCB and WCB are stored at ≤[redacted]. MCB[redacted]; WCB[redacted].

2.1.1.2 Manufacturing process

The manufacturing process for Dato consists of the following steps: WCB vial thawing/expansion culture, preculture, production culture, harvesting, [redacted] chromatography, viral inactivation ([redacted] treatment), [redacted] chromatography, [redacted] chromatography, virus removal filtration, [redacted], and final filtration/filling/testing/freezing/storage.

Critical steps are [redacted].

Process validation for Dato is performed on a commercial scale.

2.1.1.3 Safety evaluation of adventitious agents

With the exception of CHO cells (host cells), no raw materials of biological origin are used in the manufacturing process for Dato.

Purity was tested on the MCB, WCB, and LIVCA [see Section 2.1.1.1]. Bioburden testing, mycoplasma testing, *in vitro* adventitious virus testing, mouse minute virus testing, and transmission electron microscopy were performed on pre-harvest unprocessed bulk produced at commercial scale. Within the range studied, the tests detected no contamination caused by viral or non-viral adventitious infectious diseases. These tests on pre-harvest unprocessed bulk, except for transmission electron microscopy, are included as in-process controls.

A viral clearance study was performed with model viruses for the purification process. The results showed that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Mouse minute virus	Reovirus type 3	Pseudorabies virus
Viral inactivation ([redacted] treatment)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥16.15	≥7.16	≥10.23	≥16.16

2.1.1.4 Manufacturing process development

For changes made to the manufacturing process during development of Dato, comparability between pre-change and post-change Dato was confirmed in accordance with the ICH Q5E Guidelines. The global phase III study (Study TB01) used the formulation with Dato manufactured by the proposed commercial process and a formulation with Dato manufactured by the previous commercial process.

2.1.1.5 Characterization

2.1.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed. The main evaluation results of biological properties together with the evaluation results of the drug substance are described in Section "2.1.3.3.1 Structure and characterization."

Table 2. Evaluation items for characterization

Primary/higher order structure	Molecular weight, amino acid sequence, N-terminal and C-terminal amino acid sequence, post-translational modifications ([redacted]), disulfide bonds, [redacted], [redacted], secondary structure, [redacted], thermal stability
Physicochemical properties	Charge variants, size variants, protein content, extinction coefficient
Glycan structure	Glycosylation sites, N-linked glycan profile, [redacted], [redacted], O-linked glycan
Biological properties	TROP-2 binding activity
	FcγRIIIa binding affinity, FcRn binding affinity, C1q binding affinity
	Cell growth inhibitory activity
	ADCC activity, CDC activity

2.1.1.5.2 Product-related substances/Product-related impurities

Based on the characterization results in Section "2.1.1.5.1 Structure and characterization," Compound A was identified as a product-related substance. Impurity A and Impurity B were identified as product-related impurities, both of which are controlled by the specifications for Dato, the drug substance, and drug product.

2.1.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, elemental impurities, and extractables/leachables are defined as process-related impurities. Of these process-related impurities, [redacted] are considered to have a low risk of contamination into Dato or safety risk based on risk assessment results, while [redacted] have been confirmed to be removed adequately in the manufacturing process.

2.1.1.6 Control of Dato

The proposed specifications for Dato include content, description, identification (cation exchange high performance liquid chromatography [CEX-HPLC]), pH, purity testing (CEX-HPLC, size exclusion high performance liquid chromatography [SE-HPLC], and capillary electrophoresis sodium dodecyl sulfate [CE-SDS; non-reducing conditions]), bacterial endotoxins, microbial limits, [redacted], and assay (ultraviolet-visible spectrophotometry).

2.1.1.7 Stability

Table 3 shows the main stability studies for Dato.

Table 3. Summary of main stability studies for Dato

	Manufacturing Process for Dato	Number of batches	Storage condition	Test period	Storage form
Long-term	Pre-proposed commercial process	3	[redacted]°C	[redacted] months	[redacted]
	Proposed commercial process	3		[redacted] months*	
Accelerated	Proposed commercial process	3	5 ± 3°C	6 months	
Stress	Proposed commercial process	3	25 ± 2°C/60 ± 5% RH	6 months	

*, The stability testing is ongoing up to [redacted] months.

The long-term test and accelerated test showed no marked changes in quality attributes throughout the test period.

The results of the stress testing included the following: increased [redacted]; an increasing trend of [redacted], and decreased [redacted] in [redacted]; an increasing trend of [redacted], increased [redacted], and decreased [redacted] in [redacted]; a decreasing trend of [redacted] and increased [redacted] in [redacted].

Based on the above, a shelf life of [redacted] months was proposed for Dato when stored at ≤[redacted]°C using [redacted].

2.1.2 MAAA-1162a

MAAA-1162a, the drug linker intermediate, is identical to the drug linker intermediate ([redacted]) used in the manufacture of "Enhertu for Intravenous Drip Infusion 100 mg," for which the applicant is the marketing authorization holder.

2.1.3 Datopotamab deruxtecan (genetical recombination)

2.1.3.1 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], filling/freezing/storage, and testing.

Critical steps are [redacted], [redacted], [redacted], and [redacted].

Process validation for the drug substance is performed on a commercial scale.

2.1.3.2 Manufacturing process development

When changes were made to the manufacturing process in the development stage of the drug substance, comparability of the drug substance before and after the changes was confirmed in accordance with the ICH Q5E Guidelines. The global phase III study (Study TB01) used the formulation with the drug substance manufactured by the proposed commercial process and a formulation with the drug substance manufactured by the previous process.

2.1.3.3 Characterization

2.1.3.3.1 Structure and characterization

Table 4 summarizes the characterization performed.

Table 4. Evaluation items for characterization

Primary/higher order structure	Molecular weight, amino acid sequence, N-terminal and C-terminal amino acid sequence, post-translational modifications ([redacted]), disulfide bonds, [redacted], drug-to-antibody ratio, [redacted], secondary structure, [redacted], thermal stability
Physicochemical properties	Charge variants, size variants, protein content
Glycan structure	N-linked glycan profile
Biological properties	TROP-2 binding activity
	FcγRIIIa binding affinity, FcRn binding affinity, C1q binding affinity
	Cell growth inhibitory activity
	ADCC activity, CDC activity

The biological properties of the drug substance and Dato were evaluated at the same time, and the main results are summarized as follows:

- Cell growth inhibitory activity was evaluated in an *in vitro* study using the cell line BxPC-3, a human pancreatic adenocarcinoma cell line, and in an *in vivo* study using nude mice subcutaneously implanted with the human non-small cell lung cancer (NSCLC) NCI-H292 cell line. In both studies, although no cell growth inhibitory activity for Dato was observed, cell growth inhibitory activity was detected for the drug substance.
- Antibody-dependent cellular cytotoxicity (ADCC) activity for Dato and the drug substance was detected in an assay [redacted]. Given Dato's [redacted], in the *in vivo* study in xenografted mice, the applicant considers that, under *in vivo* conditions, the ADCC activity of the drug substance [redacted]. In addition, [redacted] related to [redacted] that may affect the ADCC activity [redacted] controlled by [redacted], and therefore, the homeostasis of [redacted] is assured.
- No CDC activity of Dato or the drug substance was detected in the assay using [redacted].

2.1.3.3.2 Product-related substances/Product-related impurities

On the basis of the results of characterization in Section "2.1.3.3.1 Structure and characterization," Compound B was identified as a product-related substance. Impurity K, Impurity L, and Impurity M were identified as product-related impurities, and these impurities are controlled by the specifications for the drug substance and drug product.

2.1.3.3.3 Process-related impurities

Process-related impurities were defined as Impurity N, Impurity O, Impurity P, Impurity Q, elemental impurities, and extractables/leachables. Risk assessment results has shown that, of the process-related impurities, [redacted] have a low drug substance contamination risk or safety risk, and all these impurities other than [redacted] have been confirmed to be (1) adequately removed in the manufacturing process, or (2) controlled by the specifications for MAAA-1162a, the drug substance, or the drug product.

2.1.3.4 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (hydrophobic interaction high performance liquid chromatography [HI-HPLC] and peptide mapping), osmolality, pH, purity testing (capillary zone electrophoresis, SE-HPLC, CE-SDS [reducing conditions], and reversed-phase-high performance liquid chromatography [RP-HPLC]), drug-to-antibody ratio, bacterial endotoxins, microbial limits, biological activity ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.1.3.5 Stability of drug substance

Table 5 summarizes main stability studies for the drug substance.

Table 5. Summary of main stability studies for the drug substance

	Drug substance manufacturing process	Number of batches	Storage condition	Test period	Storage form
Long-term	Pre-proposed commercial process	3	[redacted]°C	[redacted] months*	[redacted]
	Proposed commercial process	6		[redacted] months*	
Accelerated	Proposed commercial process	6	5 ± 3°C	6 months	
Stress	Proposed commercial process	6	25 ± 2°C/60 ± 5% RH	6 months	

*, The stability testing is ongoing up to [redacted] months.

The long-term tests showed no marked changes in quality attributes throughout the test period.

The accelerated test showed an increasing trend of [redacted] and a decreasing trend of [redacted] in [redacted].

The stress test results showed increased [redacted], a decreasing trend of [redacted], and decreased [redacted] in [redacted]; increased [redacted] and a decreasing trend of

[redacted] in [redacted]; increased [redacted], increased [redacted], increased [redacted], and an increasing trend of [redacted] in [redacted].

Based on the above results, a shelf life of 36 months was proposed for the drug substance when stored at ≤[redacted]°C using [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in an amber glass vial (10 mL) containing 108 mg of datopotamab deruxtecan (protein content). The drug product contains, as excipients, sucrose, L-histidine, L-histidine hydrochloride monohydrate, and polysorbate 80. Each vial is filled with an excess volume of datopotamab deruxtecan compared to the labeled amount so that, following reconstitution with 5 mL of water for injection (the resulting protein concentration is 20 mg/mL), 100 mg of datopotamab deruxtecan can be obtained.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of drug substance thawing/mixing, aseptic filtration, filling, lyophilization, capping, inspection, packaging/labeling, and product testing/storage steps.

[redacted] and [redacted] have been defined as critical steps.

Process validation is performed on a commercial scale.

2.2.3 Manufacturing process development

For changes made to the manufacturing process in the development stage of the drug product, comparability between the pre-change and post-change drug product was confirmed in accordance with the ICH Q5E Guidelines. The global phase III study (Study TB01) used a formulation manufactured by the proposed commercial process and a formulation manufactured by the previous process.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted] and capillary zone electrophoresis), osmolality, pH, purity testing (capillary zone electrophoresis, SE-HPLC, CE-SDS [reducing conditions] and RP-HPLC), drug-to-antibody ratio, water content, bacterial endotoxins, foreign insoluble matter, insoluble particulate matter, sterility, reconstitution time, biological activity ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 6 summarizes main stability studies for the drug product.

Table 6. Summary of main stability studies for the drug product

	Number of batches*1	Storage condition	Test period	Storage form
Long-term	3	5 ± 3°C	[redacted] months*2	Amber glass vial with fluororesin laminated butyl rubber stopper
Accelerated	3	25 ± 2°C/60% ± 5% RH	6 months	
Stress	3	40 ± 2°C/75 ± 5% RH	6 months	
Photostability	1	Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m^2		

*1, Formulation manufactured by the proposed commercial process using the drug substance produced by Process [redacted]; *2, the stability testing is ongoing up to [redacted] months.

The long-term test and accelerated test showed no marked changes in quality attributes throughout the test period.

The stress test showed an increasing trend of [redacted] in [redacted]; an increasing trend of [redacted], an increasing trend of [redacted], and an increasing trend of [redacted] in [redacted].

Photostability testing demonstrated that the drug product is photostable.

Based on the above results, a shelf life of 36 months was proposed for the drug product when stored at 2°C to 8°C in an amber glass vial with a fluororesin laminated butyl rubber stopper as the primary packaging.

2.3 Quality control strategy

Based on the following investigation and other data, the method for control of quality attributes of datopotamab deruxtecan comprises a combination of process parameter control, in-process control testing, and specifications [see Sections 2.1.1.5.2 and 2.1.3.3.2 for the control of product-related impurities and Sections 2.1.1.5.3 and 2.1.3.3.3 for the control of process-related impurities].

- Identification of critical quality attributes (CQAs):
  Based on information obtained in the development stage of datopotamab deruxtecan, relevant knowledge, and other factors, the CQAs presented in Table 7 were identified.

Table 7. List of identified CQAs

CQAs of Dato	[redacted], HCP, host cell DNA, [redacted], protein content, identity, pH, [redacted], appearance, purity ([redacted]), adventitious viruses, mycoplasma, bacterial endotoxins, bioburden
CQAs of MAAA-1162a	See "Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated on February 17, 2020"
CQAs of the drug substance	Appearance (color, clarity), pH, osmolality, [redacted], protein concentration, [redacted]
CQAs of the drug product	Description (appearance), identification, osmolality, pH, purity ([redacted] impurities), [redacted], water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, reconstitution time, protein concentration, [redacted], container integrity

- Process characterization:

  In the process risk assessment and process characterization studies, the effects of process parameters on the CQAs or process performance were evaluated to determine the importance of each process parameter and to select the permissible range.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Binding affinity for TROP-2 (CTD 4.2.1.1-1, 4.2.1.1-2)

The binding activity of datopotamab deruxtecan and IgG-DXd, an ADC comprising human IgG1 monoclonal antibody linked to DXd via a linker identical to that of datopotamab deruxtecan, to TROP family proteins, human TROP-1 (recombinant protein) and human TROP-2 (recombinant protein) were assessed by enzyme-linked immunosorbent assay (ELISA). Table 8 shows the binding activity of datopotamab deruxtecan and IgG-DXd.

Table 8. Binding activity of datopotamab deruxtecan and IgG-DXd to TROP-1 and TROP-2

	Binding activity*	
	Datopotamab deruxtecan	IgG-DXd
TROP-1	−0.037 ± 0.016	0.030 ± 0.036
TROP-2	3.183 ± 0.049	0.032 ± 0.034

Mean ± standard deviation; N = 3; *, absorbance at a wavelength of 450 nm

The binding affinity of datopotamab deruxtecan for CHO-K1 cells expressing human, cynomolgus monkey, mouse, and rat TROP-2 was evaluated by ELISA. Datopotamab deruxtecan bound to CHO-K1 cells expressing human and cynomolgus monkey TROP-2 with the EC_{50} values of datopotamab deruxtecan (mean [95% confidence interval (CI)], N = 3) being 110.42 ng/mL [80.32, 151.79] and 97.65 ng/mL [77.70, 122.72] for human and cynomolgus monkey TROP-2, respectively. Conversely, datopotamab deruxtecan did not bind to mouse or rat TROP-2.

3.1.2 DNA damage and induction of apoptosis (CTD 4.2.1.1-5)

Using the human pancreatic adenocarcinoma cell line CFPAC-1, the ability of datopotamab deruxtecan, IgG-DXd, Dato, and DXd to induce DNA damage or apoptosis was evaluated by Western blotting based on measurement of checkpoint kinase 1 (CHK1) phosphorylation as an indicator for DNA damage, and the expression level of truncated poly (ADP-ribose) polymerase (PARP) as an indicator for apoptosis. The results showed that DNA damage and apoptosis were induced by datopotamab deruxtecan and DXd but not by IgG-DXd or Dato.

3.1.3 ADCC activity (CTD 4.2.1.1-6)

The ADCC activity of datopotamab deruxtecan and IgG-DXd against NCI-H322 cells endogenously expressing TROP-2 was evaluated by the chromium release assay using peripheral blood mononuclear cells (PBMCs) derived from 3 healthy adult donors as effector cells. Table 9 shows the EC_{50} values and maximum ADCC activity[1)] for datopotamab deruxtecan and IgG-DXd.

Table 9. EC_{50} values and maximum ADCC activity of datopotamab deruxtecan and IgG-DXd

		Subject 1	Subject 2	Subject 3
Datopotamab deruxtecan	EC_{50}* (ng/mL)	206 [9.09, 4,660]	10.8 [6.97, 16.8]	5.27 [4.26, 6.52]
	Maximum ADCC activity (%)	25.1	32.9	64.1
IgG-DXd	EC_{50}* (ng/mL)	1,060 [0.00390, 291,000,000]	329 [77.0, 1,400]	38.3 [8.09, 182]
	Maximum ADCC activity (%)	3.13	2.20	3.69

N = 3; *, mean [95% CI]

3.1.4 Effects of growth inhibition on malignant tumor cell lines

3.1.4.1 *In vitro* (CTD 4.2.1.1-3)

The effects of growth inhibition of datopotamab deruxtecan, IgG-DXd, Dato, and DXd on CFPAC-1 and BxPC-3 cells endogenously expressing TROP-2, and human NSCLC Calu-6 cells not expressing TROP-2 were evaluated based on the ATP levels in living cells as an indicator. Table 10 shows the IC_{50} values for datopotamab deruxtecan, IgG-DXd, Dato, and DXd.

Table 10. Effects of growth inhibition of datopotamab deruxtecan, IgG-DXd, Dato, and DXd against human malignant tumor cell lines

Cell line	TROP-2 expression*	IC_{50} (nmol/L)			
		Datopotamab deruxtecan	IgG-DXd	Dato	DXd
CFPAC-1	22.1	706 [485, 1,030]	≥20,000	≥20,000	2.82 [2.36, 3.37]
BxPC-3	47.9	74.6 [69.0, 80.7]	≥20,000	≥20,000	1.58 [1.35, 1.85]
Calu-6	1.1	≥20,000	≥20,000	≥20,000	1.15 [1.07, 1.24]

Mean [95% CI]; N = 3; *, mean fluorescent intensity calculated by flow cytometry

3.1.4.2 *In vivo*

3.1.4.2.1 Breast cancer cell line (CTD 4.2.1.1-10)

Using nude mice subcutaneously implanted with human breast cancer HCC1806 cells endogenously expressing TROP-2 (N = 6/group), the antitumor effects of datopotamab deruxtecan, IgG-DXd, and Dato were evaluated. On the day when tumor volume reached approximately 170 mm^3 (Day 0), a single intravenous dose of datopotamab deruxtecan, IgG-DXd, or Dato 10 mg/kg was administered and tumor volume was calculated. On Day 18, statistically significant antitumor effects were observed in the datopotamab deruxtecan group compared with the control (vehicle[2)]), IgG-DXd, and Dato groups (Figure 1).

1) The percentage of cells in which cytotoxic effects by ADCC activity was detected
2) A 10-mmol/L acetate buffer solution containing 5% sorbitol (pH5.5)

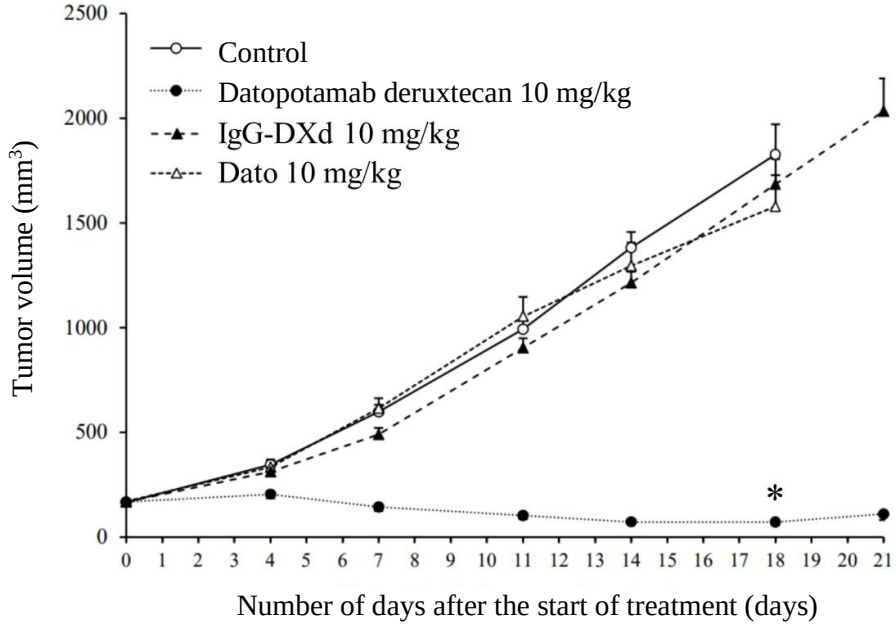


Figure 1. Antitumor effects in nude mice subcutaneously implanted with the HCC1806 cell line
N = 6; mean ± standard error; *, compared with the control group, *P* <0.0001 (Dunnett's test); compared with the IgG-DXd group and Dato group, *P* <0.0001 (Student's t-test)

3.1.4.2.2 Malignant tumor cell lines other than breast cancer (CTD 4.2.1.1-7, 4.2.1.1-8, 4.2.1.1-9)

Using nude mice subcutaneously implanted with the CFPAC-1 cell line (N = 6/group), the antitumor effect of datopotamab deruxtecan was evaluated. On the day when tumor volume reached approximately 170 mm^3 (Day 0), a single intravenous dose of datopotamab deruxtecan 0.125, 0.25, 0.5, 1, 2, or 4 mg/kg was administered and tumor volume was calculated. On Day 21, statistically significant antitumor effects were observed in the datopotamab deruxtecan 0.5, 1, 2, and 4 mg/kg groups compared with the control (vehicle[3)]) group (*P* <0.0001 for all groups; Dunnett's test).

Using nude mice subcutaneously implanted with NCI-H292 cells endogenously expressing TROP-2 (N = 6/group), the antitumor effects of datopotamab deruxtecan, IgG-DXd, and Dato were evaluated. On the day when tumor volume reached approximately 160 mm^3 (Day 0), a single intravenous dose of datopotamab deruxtecan, IgG-DXd, or Dato 10 mg/kg was administered and tumor volume was calculated. On Day 14, statistically significant antitumor effects were observed in the datopotamab deruxtecan group compared with the control (vehicle[2)]) group (*P* <0.0001, Dunnett's test), IgG-DXd group (*P* <0.0001, Student's t-test), and Dato group (*P* <0.0001, Student's t-test).

Using nude mice subcutaneously implanted with human NSCLC HCC827 cells endogenously expressing TROP-2 (N = 6/group), the antitumor effects of datopotamab deruxtecan, IgG-DXd, and Dato were evaluated. On the day when tumor volume reached approximately 200 mm^3 (Day 0), a single intravenous dose of datopotamab deruxtecan, IgG-DXd, or Dato 10 mg/kg was administered and tumor volume was calculated. On Day 21, statistically significant antitumor effects were observed in the datopotamab deruxtecan group

3) A 10-mmol/L histidine buffer solution containing 0.02% polysorbate 80 and 9% sucrose (pH6.0)

compared with the control (vehicle[2)]) group (P <0.0001, Dunnett's test), IgG-DXd group (P <0.0001, Student's t-test), and Dato group (P <0.0001, Student's t-test).

3.2 Secondary pharmacodynamics (CTD 4.2.1.2-1)

The inhibitory effects of DXd 10 μmol/L on receptors, ion channels, transporters, and enzymes (total of 86 items) were evaluated using radiolabeled ligands, etc. None of the results showed ≥50% inhibition.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3-2)

A single intravenous dose of datopotamab deruxtecan 10 or 80 mg/kg was administered to cynomolgus monkeys (N = 5/group) and the effects of datopotamab deruxtecan on the central nervous system were assessed using a functional observational battery and other methods. The results showed no effects of datopotamab deruxtecan.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3-1)

The effects of DXd on hERG potassium current were evaluated using hERG transfected CHO cells. The percentage inhibition of hERG potassium current was −4.24 ± 2.59, 0.42 ± 2.95, and −0.74 ± 4.18 at DXd 1, 3, and 10 μmol/L, respectively (N = 5; mean ± standard deviation), The results showed no effects of DXd.

3.3.2.2 Effects on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3-2)

A single intravenous dose of datopotamab deruxtecan 10 or 80 mg/kg was administered to cynomolgus monkeys (N = 5/group) to investigate the effects of datopotamab deruxtecan on heart rate, blood pressure (systolic, diastolic, and mean blood pressures), and electrocardiogram (PR, QRS, QT interval [QT], and QT interval corrected [QTc]). The results showed no effects of datopotamab deruxtecan.

3.3.3 Effects on the respiratory system (CTD 4.2.1.3-2)

A single intravenous dose of datopotamab deruxtecan 10 or 80 mg/kg was administered to cynomolgus monkeys (N = 5/group) to investigate the effects of datopotamab deruxtecan on respiratory rate and blood gases (arterial blood pH, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide, and hemoglobin oxygen saturation). The results showed no effects of datopotamab deruxtecan.

3.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about non-clinical pharmacology of datopotamab deruxtecan is acceptable.

3.R.1 Mechanism of action and efficacy of datopotamab deruxtecan

The applicant's explanation about the mechanism of action of datopotamab deruxtecan and its efficacy in breast cancer:

A single-pass transmembrane protein TROP-2 is overexpressed on the cell membrane of tumor cells such as breast cancer (e.g., *Genes Cancer.* 2015;6:84-105, *Exp Mol Pathol.* 2013;94:73-8).

Datopotamab deruxtecan is an ADC comprising Dato, a TROP-2 directed humanized IgG1 monoclonal antibody that is bound to DXd, a camptothecin derivative, which is a topoisomerase I inhibitor, via a peptide linker. Following binding to TROP-2 expressed on the cell membrane of tumor cells [see Section 3.1.1], datopotamab deruxtecan undergoes internalization followed by linker hydrolysis. It is considered that released free DXd inhibits topoisomerase I, causing DNA damage, apoptotic cell death [see Section 3.1.2], and other effects, thereby exerting antitumor effects.

Taking into account the following points, in addition to the mechanism of action described above, it is considered that datopotamab deruxtecan can be expected to be effective in the treatment of breast cancer.

- In Study TB01, a global phase III study in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer, 95% of patients with tumor tissue specimens for which TROP-2 expression status could be identified had TROP-2 expression.
- Datopotamab deruxtecan demonstrated antitumor effects in nude mice subcutaneously implanted with human breast cancer cells endogenously expressing TROP-2 [see Section 3.1.4.2.1].
- For TROP-2 negative tumor cells, after internalization into cells expressing TROP-2, datopotamab deruxtecan extracellularly releases free DXd, which may have antitumor effects against such cells (e.g., *Gynecol Oncol.* 2024;8:16-23).

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics (PK) of datopotamab deruxtecan in animals was evaluated in rats and monkeys. Human or animal biological samples were used to evaluate plasma protein binding, drug-metabolizing enzymes, transporters, and other factors of DXd, a component of datopotamab deruxtecan. In this section and Section 6, the notation "total anti-TROP-2 antibody" is collectively used to refer to any anti-TROP-2 antibody (Dato), both conjugated and unconjugated with the payload (DXd).

Datopotamab deruxtecan and the total anti-TROP-2 antibody in rat and monkey plasma were determined by ligand binding assay (lower limit of quantitation, 10 ng/mL). The assay of DXd in rat and monkey plasma was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation, 0.1 ng/mL). Electro-chemiluminescence (ECL) was used to detect anti-Dato-DXd antibodies in rat and monkey plasma. Radioactivity in monkey tissues was determined by quantitative whole-body autoradiography (lower limit of quantitation, 6.64 ng Eq./g).

4.1 Absorption

4.1.1 Single-dose studies

A single intravenous dose of datopotamab deruxtecan 0.2, 0.6, 2, or 6 mg/kg was administered to male monkeys to investigate the plasma datopotamab deruxtecan concentrations and other parameters (Table 11). Within the dose range studied, AUC_{inf} of datopotamab deruxtecan and the total anti-TROP-2 antibody increased at a rate greater than the dose ratio. The applicant considered that antigen-dependent elimination of datopotamab deruxtecan and the total anti-TROP-2 antibody through binding to TROP-2 may have become saturated with increased dosing, contributing to the above results. In most of the timepoints, DXd was below the limit of quantitation.

Anti-Dato-DXd antibodies were detected in 9 of 12 animals.

Table 11. Pharmacokinetic parameters of datopotamab deruxtecan and total anti-TROP-2 antibody (male monkeys, single intravenous dose)

Analyte	Dose (mg/kg)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Datopotamab deruxtecan	0.2	9.05 ± 0.61	1.48 ± 0.11	22.2 ± 1.6	38.4 ± 1.9
	0.6	27.5 ± 0.8	1.65 ± 0.16	21.8 ± 0.7	42.2 ± 3.2
	2	118 ± 21	1.96 ± 0.33	17.3 ± 2.8	41.6 ± 2.9
	6	392 ± 41	1.48 ± 0.32	15.4 ± 1.5	43.4 ± 0.4
Total anti-TROP-2 antibody	0.2	9.91 ± 0.80	1.67 ± 0.10	—	—
	0.6	30.8 ± 1.4	1.60 ± 0.26	—	—
	2	125 ± 26	1.50 ± 0.23	—	—
	6	423 ± 52	1.47 ± 0.18	—	—

Mean ± standard deviation; "—," not calculated; N = 3

4.1.2 Repeated-dose studies

Intravenous doses of datopotamab deruxtecan 20, 60, or 200 mg/kg were administered to male and female rats every 3 weeks for 3 months to investigate plasma datopotamab deruxtecan concentrations and other parameters (Table 12). Within the dose range studied, C_0 and AUC_{21day} of datopotamab deruxtecan, total anti-TROP-2 antibody, or DXd increased roughly at a rate greater than the dose ratio. No clear sex differences were noted.

Anti-Dato-DXd antibodies were detected in 1 of 24 animals.

Table 12. Pharmacokinetic parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd (male and female rats, 3-month repeated intravenous dose)

Analyte	Dose (mg/kg)	Dosing day (Day)	C_0 (μg/mL)		AUC_{21day} (μg·day/mL)		$t_{1/2}$ (day)	
			Male	Female	Male	Female	Male	Female
Datopotamab deruxtecan	20	1	445 ± 21.2	459 ± 32.7	1,830 ± 126	1,950 ± 145	7.45 ± 2.99	9.71 ± 0.252
		64	681 ± 44.8	635 ± 55.5	2,720 ± 968	2,430 ± 844	10.1 ± 6.09	9.55 ± 4.17
	60	1	1,580 ± 43.2	1,610 ± 88.6	6,000 ± 332	6,260 ± 434	6.91 ± 0.807	6.87 ± 2.66
		64	2,400 ± 92.7	2,130 ± 303	10,200 ± 2,470	7,290 ± 965	12.9 ± 4.31	10.7 ± 1.14
	200	1	4,830 ± 230	4,600 ± 336	18,800 ± 897	18,600 ± 423	8.86 ± 0.204	7.69 ± 0.877
		64	6,660 ± 376	5,510 ± 375*	28,400 ± 5,470	20,600 ± 5,460*	11.3 ± 1.90	11.8 ± 4.13*
Total anti-TROP-2 antibody	20	1	412 ± 29.8	422 ± 30.6	2,100 ± 147	2,140 ± 117	8.67 ± 2.68	11.6 ± 0.295
		64	657 ± 75.0	617 ± 65.4	3,230 ± 1,170	2,920 ± 1,070	12.9 ± 7.02	11.1 ± 5.48
	60	1	1,600 ± 50.2	1,720 ± 97.0	6,990 ± 444	7,380 ± 472	8.09 ± 0.818	8.18 ± 2.60
		64	2,550 ± 107	2,110 ± 185	12,000 ± 3,010	8,690 ± 1,060	15.8 ± 5.93	12.7 ± 1.65
	200	1	4,870 ± 74.6	4,800 ± 262	22,800 ± 1,250	22,800 ± 816	9.30 ± 0.391	8.63 ± 1.45
		64	6,840 ± 583	5,090 ± 683*	33,400 ± 6,070	24,600 ± 7,230*	13.8 ± 3.83	14.7 ± 5.67*
			C_{max} (ng/mL)		AUC_{21day} (ng·day/mL)		$t_{1/2}$ (day)	
			Male	Female	Male	Female	Male	Female
DXd	20	1	0.163 ± 0.0219	0.128 ± 0.0150	0.631 ± 0.0575	0.523 ± 0.112	—	—
		64	0.327 ± 0.102	0.278 ± 0.0771	2.40 ± 0.395	0.826 ± 0.0494	14.4 ± 16.8	—
	60	1	0.466 ± 0.0318	0.403 ± 0.0947	3.41 ± 0.392	3.03 ± 0.726	5.82, 5.85	3.43
		64	1.08 ± 0.422	0.901 ± 0.106	5.97 ± 1.49	4.28 ± 0.783	3.43 ± 0.608*	3.35 ± 0.508*
	200	1	2.44 ± 0.221	1.49 ± 0.198	10.8 ± 0.411	8.86 ± 0.729	3.22 ± 0.217	4.08 ± 1.63
		64	4.06 ± 0.809	3.25 ± 1.25*	19.9 ± 3.37	13.0 ± 0.269*	5.84 ± 0.879	5.41 ± 2.59*

Mean ± standard deviation; "—," not calculated; N = 4 (individual values for N = 1 or 2); *, N = 3

4.2 Distribution

4.2.1 Tissue distribution

A single intravenous dose of ^{14}C-labeled DXd 1 mg/kg was administered to male monkeys to investigate the distribution of radioactivity in various tissues. Radioactivity was widely distributed across the tissues, and in the majority of tissues including blood, the radioactivity level reached its maximum by approximately 1 hour post-dose. Tissues with particularly high radioactivity levels compared to the maximum plasma radioactivity concentration (65.7 ng Eq./g) were as follows: large intestine wall (42,357, maximum radioactivity in the tissue [ng Eq./g]; the same applies hereinafter), small intestine wall (31,436), cecum mucosa (11,441), gallbladder (4,714), urinary bladder wall (1,247), kidney cortex (875), kidney (799), liver (497), kidney medulla (471), brown fat (346), pigmented skin (296), white fat (inguinal) (235), ciliary body (227), seminal vesicle (201), sclera (179), and aorta (146). Conversely, radioactivity levels were below the lower limit of quantitation at all timepoints in the brain, anterior chamber, cornea, lens, vitreous humor, pituitary gland, and spinal cord. While radioactivity disappeared in most tissues by 96 hours post-dose, radioactivity was detected in the kidney cortex (104 ng Eq./g; the same applies hereinafter), kidney (74.8), liver (20.2), kidney medulla (11.9), small intestine wall (10.4), esophagus wall (7.85), glandular areas of the stomach wall (7.60), and spleen (7.49). Tissue distribution studies for datopotamab deruxtecan and Dato have not been conducted.

4.2.2 Plasma protein binding and distribution in blood cells

The applicant submitted results data on plasma protein binding and distribution in blood cells that had been evaluated at the time of the initial approval of trastuzumab deruxtecan (genetical recombination) (T-DXd); therefore, details of the data are not discussed here.[4)]

4.2.3 Placental transfer and fetal transfer

Neither placental transfer nor fetal transfer of datopotamab deruxtecan have been studied.

The applicant explained that since human IgG antibodies are reported to cross the placenta to the fetus (*The Japanese journal of medical technology*. 2021;70:525-8), datopotamab deruxtecan, which comprises IgG1 subclass humanized antibody, may also cross the placenta to the fetus.

4.3 Metabolism

4.3.1 Stability in plasma

Datopotamab deruxtecan (10 or 100 μg/mL) was incubated with mouse, rat, monkey, or human plasma, or a phosphate-buffered saline containing 1% bovine serum albumin (BSA) at 37°C for 21 days to investigate the stability of datopotamab deruxtecan in plasma. The percentage of DXd released from datopotamab deruxtecan was 1.4% to 1.5% (mouse), 1.7% to 1.8% (rat), 5.5% to 6.5% (monkey), 3.8% to 5.0% (human), and 0.2% (phosphate-buffered saline containing 1% BSA).[5)] The applicant explained that the results suggest that only a limited amount of DXd is released from datopotamab deruxtecan to plasma, and that datopotamab deruxtecan exists in plasma in a stable manner.

4.3.2 *In vitro*

In addition to the data evaluated at the initial approval of T-DXd, the applicant submitted the results data on *in vitro* metabolism of DXd as shown below. Details of data that were evaluated at the time of the initial approval of T-DXd are not discussed here.[4)]

Based on the data already evaluated at the time of the initial approval of T-DXd, and the following evaluation results, the applicant explained that primarily cytochrome P450 (CYP)3A is involved in the oxidative metabolism of DXd, and DXd does not seem to undergo significant metabolism by uridine diphosphate glucuronosyl transferase (UGT). Pharmacokinetic drug interactions between datopotamab deruxtecan and CYP3A inhibitors will be discussed in Section "6.R.2 Pharmacokinetic drug interactions with CYP3A, P-gp, BCRP, and OATP1B inhibitors."

- Rat, monkey, human (wild type), or human (variant, *UGT1A1*28/*28*[6)]) liver microsomes were incubated with DXd (10, 100, or 1,000 ng/mL) at 37°C for 1 hour in the presence of uridine diphosphate glucuronic acid (UDPGA) to investigate the metabolism of DXd by UGT. In all of the animal liver microsomes, the residual percentage of DXd was ≥92.0%.

4) See "Review Report on Enhertu for Intravenous Drip Infusion 100 mg, dated on February 17, 2020" and other sources.
5) The percentage of DXs released from datopotamab deruxtecan 10 or 100 μg/mL in phosphate-buffered saline containing 1% BSA was 0.2% for both concentrations.
6) Homozygous for *UGT1A1*28*

4.3.3 *In vivo*

In addition to the data evaluated at the time of the initial approval of T-DXd, the applicant submitted the results data for urinary, fecal, and biliary metabolites following administration of a single intravenous dose of ^{14}C-labeled DXd 1 mg/kg to bile-duct non-cannulated and cannulated monkeys, and the following results were obtained. Details of data that were evaluated at the time of the initial approval of T-DXd are not discussed here.[4)]

- In bile-duct non-cannulated monkeys, mainly unchanged DXd was detected in urine samples collected up to 6 hours post-dose, accounting for 4.8% of the total radioactivity administered.
- In bile-duct non-cannulated monkeys, mainly unchanged DXd was detected in fecal samples collected up to 24 hours post-dose, accounting for 34.2% of the total radioactivity administered.
- In bile-duct cannulated monkeys, mainly unchanged DXd was detected in bile samples collected up to 6 hours post-dose, accounting for 54.9% of the total radioactivity administered.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

In addition to the data evaluated at the time of the initial approval of T-DXd, results data on excretion of DXd as shown below were submitted. Details of data that were evaluated at the time of the initial approval of T-DXd are not discussed here.[4)]

Based on the results data that were evaluated at the time of initial approval of T-DXd and discussion results below, the applicant considers that DXd and its metabolites are mainly excreted in feces via bile.

- Following single intravenous dose administration of ^{14}C-labeled DXd 1 mg/kg to male monkeys, 5.4% (urine) and 61.8% (feces) of the total radioactivity administered was detected up to 4 days post-dose.
- Following single intravenous dose administration of ^{14}C-labeled DXd 1 mg/kg to bile-duct cannulated male monkeys, 4.8% (urine), 0.1% (feces), and 70.7% (bile) of the total radioactivity administered was detected up to 4 days post-dose.

4.4.2 Excretion in breast milk

Excretion of datopotamab deruxtecan and DXd in breast milk has not been studied.

The applicant explained that there is a report that human IgG antibody is excreted in breast milk (*Neurol Neuroimmunol Neuroinflamm.* 2020;7:e769). Because its antibody component is an IgG1 subclass humanized antibody, datopotamab deruxtecan may also be excreted in breast milk.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme inhibition

The applicant submitted results data on metabolic enzyme inhibition by DXd that had been evaluated at the time of the initial approval of T-DXd; therefore, details of the data are not discussed here.[4)]

The applicant's explanation:

Taking into account the results data that had been evaluated at the time of the initial approval of T-DXd, as well as C_{max} of DXd (5 nmol/L[7)]) at the proposed dosage regimen of datopotamab deruxtecan, it is unlikely that pharmacokinetic drug interactions will occur due to inhibition of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) by DXd when datopotamab deruxtecan is used clinically.

4.5.2 Enzyme induction

The applicant submitted results data on metabolic enzyme induction by DXd that had been evaluated at the time of the initial approval of T-DXd; therefore, details of the data are not discussed here.[4)]

The applicant's explanation:

Taking into account the results data that had been evaluated at the time of the initial approval of T-DXd, as well as the C_{max} of DXd (5 nmol/L[7)]) at the proposed dosage regimen of datopotamab deruxtecan, it is unlikely that pharmacokinetic drug interactions will occur via induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) by DXd when datopotamab deruxtecan is used clinically.

4.5.3 Transporters

The applicant submitted results data on transporter-mediated pharmacokinetic drug interactions by DXd that had been evaluated at the time of the initial approval of T-DXd; therefore, details of the data are not discussed here.[4)]

The applicant's explanation based on the results data that had been evaluated at the time of the initial approval of T-DXd:

- Although DXd has been shown to be a substrate of P-glycoprotein (P-gp), BCRP, organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug and toxin extrusion (MATE)2-K, and multidrug resistance associated protein (MRP)1, given the insignificant contribution of renal excretion in DXd clearance [see Section 4.4.1] and other factors, it is unlikely that pharmacokinetic drug interactions will pose a problem when datopotamab deruxtecan is used clinically in combination with MATE2-K or MRP1 inhibitor.
- Although DXd has been shown to inhibit transport of substrates of organic anion transporter (OAT)1 and OATP1B1, given the C_{max} of DXd (5 nmol/L[7)]) at the proposed dosage regimen of datopotamab deruxtecan, it is unlikely that pharmacokinetic drug interactions will occur due to inhibition of OAT1 and OATP1B1 by DXd when datopotamab deruxtecan is used clinically.

The pharmacokinetic drug interactions of datopotamab deruxtecan with P-gp, BCRP, and OATP1B inhibitors will be discussed in Section "6.R.2 Pharmacokinetic drug interactions with CYP3A, P-gp, BCRP, and OATP1B inhibitors."

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7) The C_{max} value on Day 43 following intravenous administration of datopotamab deruxtecan 6.0 mg/kg Q3W in the global phase I study (Study TP01).

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacokinetics is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted using datopotamab deruxtecan, and the acute toxicity and approximate lethal dose of datopotamab deruxtecan were evaluated in repeated-dose toxicity studies in rats (CTD 4.2.3.2-1) and cynomolgus monkeys (CTD 4.2.3.2-3) (Table 13). No deaths or acute symptoms occurred at the maximum dose level in rats or cynomolgus monkeys. Based on the results, the approximate lethal dose of datopotamab deruxtecan was determined to be >200 mg/kg in rats and >80 mg/kg in cynomolgus monkeys.

5.2 Repeated-dose toxicity

Three-month repeated-dose toxicity studies were conducted in rats and cynomolgus monkeys (Table 13). Major toxicity or abnormal findings reported in both rats and cynomolgus monkeys are as follows: low body weight, single cell necrosis of the crypt epithelium in the small intestine, renal tubular degeneration, lung hemorrhage/inflammatory cell infiltration/foamy macrophage accumulation, thymus atrophy, necrosis/erosion of skin epidermis/appendages. Those reported only in rats are as follows: abnormal kidney function parameters, single cell necrosis of the crypt epithelium in the large intestine, seminiferous tubule epithelial degeneration/necrosis, decreased bone marrow hematopoietic cells, atrophy of the periarteriolar lymphoid sheath (PALS) in the spleen, low leukocyte parameters, atrophy of mammary gland epithelium in male rats, single cell necrosis of mucosal epithelium in the vagina, and increased number of atretic follicles. Those reported only in monkeys are as follows: degeneration/necrosis of the corneal epithelium, skin inflammation, low erythrocyte parameters, decreased platelet count, high fibrinogen, pulmonary edema, high surfactant protein D (SP-D) in blood, decreased partial pressure of oxygen in blood, and decreased hemoglobin oxygen saturation.

The applicant's explanation about toxicity and anormal findings observed in the immune system, incisors, erythrocyte/leukocyte parameters, coagulation system, and joints in rats or cynomolgus monkeys:

- Anomalies in renal damage-related parameters and decreased immune system parameters were observed in rats and cynomolgus monkeys. Adverse events related to these findings were reported in the datopotamab deruxtecan group in Study TB01; however, given that the incidence and severity of these events were low, safety risks in humans are considered to be low.
- Necrosis and degeneration of incisors were observed in rats. These are changes unique to rats in which incisors continuously grow throughout the animal's life; therefore, it is considered that these findings are not applicable to adult humans whose tooth formation has already completed.
- Low levels of erythrocyte parameters and blood albumin and high levels of leukocyte parameters and fibrinogen were reported in cynomolgus monkeys. These values, which are within the range of historical control data, are of low toxicological significance.

- In relation to gait abnormalities in cynomolgus monkeys, tissue degeneration in the hip joint articular surface and synovial cell hyperplasia were observed. Currently, there have been no reports suggesting that TROP-2 is expressed in joints; therefore, it is unlikely that these findings are direct effects of datopotamab deruxtecan.

The necessity of cautionary statements regarding toxicity findings in the cornea, lung, hematopoietic system, and gastrointestinal tracts based on the incidence of adverse events in the clinical studies will be described in Sections "7.R.3.3 Eye disorders," "7.R.3.4 ILD," "7.R.3.6 Myelosuppression," and "7.R.3.7 Gastrointestinal disorders," respectively.

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	STD_{10} or HNSTD (mg/kg)	CTD
Male/ female rats (Sprague Dawley)	IV	3 months (Q3W) + 2-month recovery period	0,[*1] 20, 60, 200	At ≥20, increased tingible body macrophages in the thymus (males) At ≥60, incisor overgrowth,[*2] single cell necrosis in the crypt epithelium of the rectum, necrosis of ameloblast of incisors (males/females); incisor crushing,[*2] incisor whitening,[*2] renal tubular hyaline cast/epithelial regeneration, single cell necrosis in the crypt epithelium of the duodenum (males); low body weight/food consumption, increased tingible body macrophages in the thymus, single cell necrosis in the crypt epithelium of the jejunum (females) At 200, loss of fur,[*2] high urine protein, low reticulocyte count, high blood urea nitrogen, small thymus size, low thymus weight, low epididymis weight, renal glomerular podocyte degeneration, lung hemorrhage/infiltration of neutrophil in alveolus/alveolar epithelium regeneration, decreased erythroblastic/granulocytic cells in bone marrow, single cell necrosis in the crypt epithelium of the ileum/cecum, single cell necrosis in hair follicles of the skin, abnormal incisor dentin formation, single cell necrosis in incisor enamel organ (males/females); low food consumption, low neutrophil count, low blood albumin, low A/G ratio, lung spots, single cell necrosis in the crypt epithelium of the jejunum, necrosis of skin epidermis, testicular seminiferous epithelium degeneration/seminiferous tubule atrophy, epididymis cell debris, decreased sperm count in the epididymis, single cell necrosis in epithelium of the ductus epididymis, atrophy of mammary gland epithelium (males); incisor crushing,[*2] incisor whitening,[*2] smudge of periorbital area, low white blood count, low lymphocyte count, cecum black contents, renal tubular hyaline cast/epithelial regeneration, foamy alveolar macrophage accumulation in the lung, thymic cortex atrophy, atrophy of PALS in the spleen, single cell necrosis in the crypt epithelium of the duodenum, increased number of atretic follicles in the ovary, single cell necrosis of mucosal epithelium in the vagina, incisor hemorrhage in root/necrosis in root (females) At 60, gingivitis (males)	>200 (STD_{10})	4.2.3.2-1

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	STD_{10} or HNSTD (mg/kg)	CTD
				Post-recovery period[*3] At 200, small testis size, low testis/epididymis weight, testicular seminiferous epithelium degeneration/seminiferous tubule atrophy (males)		
Male/ female cynomolgus monkeys	IV	3 months (Q3W) + 2-month recovery period	0,[*1] 10, 30, 80	At ≥10, single cell necrosis in the crypt epithelium of the duodenum (males/females) At ≥30, skin black discoloration,[*2] low body weight, single cell necrosis of epithelium in the crypt epithelium of the jejunum, thymus atrophy[*4] (males/females); lung opacity, low partial pressure of oxygen in blood, low urine pH, high ketone bodies in urine, lung brown focus, single cell necrosis in the crypt epithelium of the ileum, foamy alveolar macrophage accumulation/edema/interstitial inflammation in the lung (males); cornea brown pigmentation,[*5] high fibrinogen, brown pigmentation of the skin epidermis, single cell necrosis in corneal epithelium (females) At 80, low blood albumin, low A/G ratio, high blood globulin, corneal epithelium atrophy (males/females); skin eruption in the neck, abdomen, and thigh, cornea brown pigmentation,[*5] single cell necrosis in corneal epithelium, vacuolation in corneal epithelium, anisokaryosis in proximal tubule in the kidney (males); knee excoriation, inguinal/sural skin erosion/crust, incomplete eyelid closure, abnormal gait, low urine pH, high ketone bodies in urine, low red blood cell count, low hemoglobin concentration, low hematocrit, high reticulocyte count, high white blood cell count, high neutrophil count, skin red discoloration,[*2] right hip joint abrasion/crust,[*2] right joint articular capsule thickening,[*2] right axillary lymph node swelling,[*2] right axillary plasma cell infiltration in the medulla, single cell necrosis in the crypt epithelium of the ileum, brown pigmentation in the skin epidermis, skin erosion,[*5] skin epidermis/dermis inflammatory cell infiltration, skin crust, skin fibrosis of dermis, mononuclear cell infiltration in dermis, right hip joint fibrocartilage formation in the articular surface/articular surface erosion/synovial cell hyperplasia/fibrous thickening of articular capsule (females) At 30, high SP-D in blood, low hemoglobin oxygen saturation, lung red focus, high lung weight, alveolus hemorrhage/alveolus inflammation (males) At 10, low platelet count (males/females)	10 (HNSTD)	4.2.3.2-3
				Post-recovery period[*3] At ≥30, brown pigmentation of the skin epidermis (males/females) At 80, corneal brown pigmentation (males/females)		

*1, A 10-mmol/L-histidine buffer (pH6.0) containing 9% sucrose and 0.02% polysorbate 80; *2, observation of clinical signs or necropsy findings; *3, findings that are unlikely to be reversible; *4, excluding females in the 80 mg/kg group; *5, including observation of clinical signs, ophthalmological examination, or histological examination findings

5.3 Genotoxicity

The applicant submitted results data on the genotoxicity of DXd that had been evaluated at the time of the initial approval of T-DXd; therefore, details of the data are not discussed here.[4)]

5.4 Carcinogenicity

No carcinogenicity studies were conducted because datopotamab deruxtecan is an antineoplastic agent intended to be used for the treatment of patients with advanced cancer.

5.5 Reproductive and developmental toxicity

In the repeated-dose toxicity in rats (CTD 4.2.3.2-1), abnormal spermatogenesis and increased number of atretic follicles were reported (Table 13). It has been demonstrated that DXd is genotoxic.[4)] In addition, in rat and rabbit toxicity studies of irinotecan, which has a structure similar to that of DXd and is a topoisomerase I inhibitor, like DXd, irinotecan is reported to be teratogenic.

The above findings suggest that datopotamab deruxtecan may have adverse effects on spermatogenesis and fetal development; therefore, the applicant explained its plan to include the cautionary statements shown below:

- Advise females of reproductive potential to use effective contraception during treatment with datopotamab deruxtecan and for 7 months after the last dose, and advise male with female partners of reproductive potential to use effective contraception during treatment with datopotamab deruxtecan and for 4 months after the last dose.[8)]
- Datopotamab deruxtecan may be administered to females who are or may be pregnant only when the treatment benefits are determined to outweigh the risks.

5.6 Other toxicity studies

5.6.1 Local tolerance

The local tolerance of datopotamab deruxtecan was evaluated based on the results of the 3-month repeated intravenous-dose toxicity studies in rats (CTD 4.2.3.2-1) and cynomolgus monkeys (CTD 4.2.3.2-3). No irritation related to datopotamab deruxtecan was observed at 20 mg/mL, a concentration greater than the maximum clinical dose level; therefore, the applicant explained that it is unlikely that datopotamab deruxtecan will cause local tolerance-related concerns.

5.6.2 Tissue cross-reactivity studies

Tissue cross-reactivity studies were conducted using normal tissue from humans and cynomolgus monkeys. The results indicated binding of datopotamab deruxtecan to the plasma membrane of multiple tissues (Table 14). The applicant explained that organs/tissues found to be positive for staining only in their cytoplasmic components or cytoplasmic granules are in the cytoplasm to which datopotamab deruxtecan will not reach; therefore, these results are considered to be of low toxicological significance. In addition, tissues found to be positive for staining only in the plasma membrane of human tissues have a low incidence of adverse events, with the exception of cornea, in the datopotamab deruxtecan group in Study TB01; therefore, it is considered that there are no significant safety concerns.

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8) In accordance with the "Guidance on the need for contraception related to the use of pharmaceuticals" (PSEHB/PED Notification No. 0216-1 and PSEHB/PSD Notification No. 0216-1, dated February 16, 2023), a contraception period of 7 months for females and 4 months for males were selected based on the $t_{1/2}$ data in humans (4.93 days for datopotamab deruxtecan and 5.83 days for DXd) [see Section 6.2.1.2].

Table 14. Tissue cross-reactivity studies

Test system	Test method	Results	CTD
Human normal tissue	Frozen sections from human tissue were reacted with datopotamab deruxtecan (2 and 10 μg/mL), followed by evaluation using immunohistochemical staining (indirect method)	**Staining in plasma membrane** Urinary bladder mucosa, breast glands*/ducts,* eye conjunctiva/cornea,* fallopian tube mucosa, esophagus mucosa, stomach mucosa, kidney tubules*/Bowman's capsule,* liver bile ducts, lung alveolus, pancreas ducts/acini, placenta amnion,* salivary gland ducts, skin epidermis/adnexa, thymus reticular tissue*/Hassall's corpuscle,* thyroid follicles, tonsil mucosa/crypt, ureter mucosa, uterus cervical mucosa/glands, uterus endometrium glands/myometrium,* mesothelium of fallopian tube,* decidual cells in placenta* **Staining in cytoplasmic elements only** lung bronchiole, ovary surface layer, parathyroid glands, pituitary endocrine glands/Rathke's cleft cyst, placenta trophoblast, prostate glands/ducts, salivary gland acini, Schwann cells in peripheral nerve/spinal cord	4.2.3.7.7-1
Cynomolgus monkey normal tissue	Frozen sections from cynomolgus monkey tissue were reacted with datopotamab deruxtecan (2 and 10 μg/mL), followed by evaluation using immunohistochemical staining (indirect method)	**Staining in plasma membrane** Urinary bladder mucosa, eye conjunctiva, fallopian tube mucosa, esophagus mucosa, stomach mucosa, small intestine mucosa, liver bile ducts, lung alveolus, pancreas ducts/acini, salivary gland ducts/acini, skin epidermis/adnexa, testis ductus deferens, thyroid follicles, tonsil mucosa/crypt, ureter mucosa, uterus cervical mucosa/glands, uterus endometrium mucosa/glands **Staining in cytoplasmic elements only** Mammary glands/ducts, kidney tubules/Bowman's capsule/pelvic epithelium, lung bronchiole, ovary surface layer, parathyroid glands, thymopharyngeal ducts, pituitary endocrine glands, placenta amniotic membrane, prostate glands/ducts/urethra, thymus squamous/Hassall's corpuscle/thymopharyngeal ducts, Schwann cells in the cerebellum/spinal cord	4.2.3.7.7-2

*, Specific staining was observed only in plasma membrane of human tissue.

5.6.3 Cytokine release studies

The ability of datopotamab deruxtecan to release cytokine was evaluated using human PBMC and whole blood. Datopotamab deruxtecan promoted production of tumor necrosis factor (TNF)-α and macrophage inflammatory protein (MIP)-1β from human PBMC (Table 15). Because infusion-related reactions, adverse events related to cytokine release, occurred in a certain percentage of subjects in the datopotamab deruxtecan group in Study TB01, the applicant explained that a cautionary statement regarding infusion-related reactions associated with datopotamab deruxtecan will be included.

The necessity of the cautionary statements based on the incidence of adverse events in the clinical studies and other factors will be described in Section "7.R.3.5 Infusion-related reactions."

Table 15. Cytokine release studies

Test system	Test method	Results	CTD
Human PBMC	Datopotamab deruxtecan or Dato 0,* 0.15, 1.5, 15, or 150 μg/mL was incubated with human PBMC for 48 hours, and cytokine (TNF-α, IFN-γ, IL-2, IL-6, IL-10, MIP-1β, and IP-10) concentrations were measured	**Datopotamab deruxtecan** Increased TNF-α and MIP-1β concentrations **Dato** Increased TNF-α, IL-6, IL-10, and MIP-1β concentrations	4.2.3.7.7-7 (reference)
Human whole blood	Datopotamab deruxtecan or Dato 0,* 0.15, 1.5, 15, or 150 μg/mL was incubated with human whole blood for 24 hours, and cytokine (TNF-α, IFN-γ, IL-2, IL-6, IL-10, MIP-1β, and IP-10) concentrations were measured	**Datopotamab deruxtecan and Dato** No increase in cytokine concentrations	4.2.3.7.7-8 (reference)

*, Phosphate-buffered saline

5.6.4 Repeated-dose toxicity study and phototoxicity study of DXd

The applicant submitted data on the general toxicity and phototoxicity of DXd that had been evaluated at the time of the initial approval of T-DXd; therefore, details of the data are not discussed here.[4)]

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the toxicity of datopotamab deruxtecan is acceptable.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Datopotamab deruxtecan and total anti-TROP-2 antibody in human plasma were determined by ligand binding assays (lower limit of quantitation, 20 or 100 ng/mL[9)] for both datopotamab deruxtecan and total anti-TROP-2 antibody), and DXd in human plasma was determined by LC-MS/MS (lower limit of quantitation, 10 pg/mL). Anti-Dato-DXd antibodies and neutralizing antibodies to datopotamab deruxtecan in human plasma were detected by ECL and cell-based assays, respectively.

6.2 Clinical pharmacology

6.2.1 Global studies

6.2.1.1 Global phase I study (CTD 5.3.3.2-1, Study TP01 [NSCLC cohort, ongoing since February 2018, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in 210 patients (N = 210 for PK analysis) with unresectable advanced or recurrent NSCLC for which no standard treatment was available to investigate the PK, etc. of datopotamab deruxtecan. Subjects were to receive datopotamab deruxtecan 0.27 to 10.0 mg/kg intravenously in 3-week cycles, each consisting of 21 days. Plasma datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd concentrations were evaluated.

Table 16 shows the PK parameters for datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd. Within the dose range studied, datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd exposures increased in

9) The lower limit of quantitation was 20 ng/mL in Study TP01, and 100 ng/mL in Studies TL01, TL05, and TB01.

a roughly dose-dependent manner. Datopotamab deruxtecan exposure reached steady state by Cycle 3, with an accumulation ratio[10)] of 1.29 for datopotamab deruxtecan.

Table 16. Pharmacokinetic parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd

Dosing day	Analyte	Dose (mg/kg)	N	C_{max} (μg/mL[*1])	AUC_{21day} (μg·day/mL[*2])	t_{max}[*3] (h)	$t_{1/2}$ (day)
Cycle 1, Day 1	Datopotamab deruxtecan	0.27[*4]	4	6.17 ± 1.52	12.6 ± 4.72	1.83 (1.65, 2.00)	1.57 ± 0.330
		0.5	5	11.8 ± 2.48	27.8 ± 8.24	1.78 (1.77, 6.97)	1.98 ± 0.488
		1.0	6	25.4 ± 4.14	88.4 ± 26.0	1.87 (1.67, 5.03)	3.06 ± 0.758
		2.0	6	51.6 ± 10.4	155 ± 49.6	1.77 (1.67, 2.12)	2.96 ± 0.777
		4.0	49	103 ± 22.4	436 ± 129	2.02 (1.55, 7.08)	4.72 ± 1.11[*5]
		6.0	50	148 ± 29.9	677 ± 279[*6]	2.03 (1.65, 192)	4.82 ± 0.975[*7]
		8.0	74	194 ± 39.7	882 ± 229[*8]	1.97 (0.800, 7.13)	5.54 ± 1.34[*8]
		10.0[*4]	8	271 ± 36.4	1,280 ± 187	3.08 (1.83, 6.92)	5.19 ± 1.35
	Total anti-TROP-2 antibody	0.27[*4]	4	6.40 ± 1.48	13.6 ± 4.71	2.56 (1.75, 3.25)	1.56 ± 0.360
		0.5	5	12.5 ± 2.28	30.5 ± 7.51	1.78 (1.77, 6.97)	2.21 ± 0.543
		1.0	6	28.9 ± 2.78	98.3 ± 27.3	1.90 (1.67, 5.02)	3.16 ± 0.767
		2.0	6	51.7 ± 7.51	162 ± 41.7	1.78 (1.67, 3.22)	3.12 ± 0.836
		4.0	49	106 ± 24.7	445 ± 112[*7]	2.02 (1.55, 7.08)	4.90 ± 0.893[*7]
		6.0	50	150 ± 31.3	699 ± 289	2.00 (1.65, 192)	5.06 ± 1.15[*6]
		8.0	74	198 ± 41.6	948 ± 237[*8]	1.97 (0.800, 7.03)	6.02 ± 1.56[*8]
		10.0[*4]	8	268 ± 41.0	1,300 ± 229	2.01 (1.83, 4.92)	5.73 ± 1.82
	DXd	0.27[*4]	4	0.190 ± 0.0760	0.834 ± 0.364[*9]	23.3 (5.00, 23.8)	2.54
		0.5	5	0.261 ± 0.127	1.17, 2.62	24.3 (23.7, 30.5)	2.89, 4.70
		1.0	6	0.506 ± 0.152	2.73 ± 0.835	23.3 (3.08, 24.1)	4.40 ± 1.01
		2.0	6	2.77 ± 4.38	12.6 ± 17.2	23.0 (4.98, 25.7)	4.22 ± 0.836
		4.0	49	1.79 ± 0.770	11.6 ± 4.04[*5]	7.17 (2.95, 49.0)	5.47 ± 0.817[*10]
		6.0	50	3.13 ± 2.23	19.2 ± 6.74[*11]	23.2 (3.05, 94.5)	5.50 ± 0.851[*12]
		8.0	76	3.62 ± 1.81	25.5 ± 11.9[*8]	23.6 (3.05, 98.7)	6.25 ± 1.29[*13]
		10.0[*4]	8	4.48 ± 2.66	32.6 ± 10.5	15.5 (4.92, 94.5)	6.82 ± 2.46
Cycle 3, Day 1	Datopotamab deruxtecan	0.5	1	9.69	24.1	0.783	2.18
		1.0	5	27.0 ± 3.35	91.8 ± 36.0	2.98 (0.717, 5.03)	2.87 ± 0.877
		2.0	4	56.6 ± 11.0	189 ± 82.7	0.875 (0.817, 5.13)	3.20 ± 1.00
		4.0	31	108 ± 32.9	518 ± 129	1.83 (0.667, 7.20)	5.37 ± 1.25[*14]
		6.0	31	160 ± 34.4	861 ± 251	0.900 (0.633, 7.07)	5.55 ± 1.15
		8.0	32	215 ± 53.2	1,270 ± 338[*14]	1.44 (0.0333, 6.88)	6.90 ± 1.71[*15]
	Total anti-TROP-2 antibody	0.5	1	10.3	28.1	0.783	2.38
		1.0	5	28.2 ± 3.12	103 ± 35.5	0.733 (0.667, 5.03)	3.09 ± 0.949
		2.0	4	77.3 ± 38.6	199 ± 81.8	1.93 (0.833, 3.17)	3.38 ± 1.10
		4.0	31	107 ± 17.5	539 ± 144	1.73 (0.600, 7.00)	5.60 ± 1.22[*14]
		6.0	31	165 ± 36.4	928 ± 264	0.900 (0.633, 6.92)	5.91 ± 1.21
		8.0	32	215 ± 55.0	1,380 ± 409[*16]	1.57 (0.650, 6.85)	7.42 ± 1.66[*16]
	DXd	0.5	1	0.164	—	47.2	—
		1.0	5	0.575 ± 0.176	3.70 ± 1.54	23.5 (22.2, 47.5)	4.60 ± 0.983
		2.0	4	2.37 ± 2.81	13.1 ± 12.7	24.3 (23.1, 52.1)	5.04 ± 1.15
		4.0	31	1.69 ± 0.686	12.4 ± 4.80[*14]	7.08 (2.95, 74.9)	6.15 ± 1.01[*17]
		6.0	31	2.63 ± 0.918	19.2 ± 6.51[*15]	7.23 (4.83, 51.2)	6.88 ± 1.55[*15]
		8.0	32	3.41 ± 1.49	25.9 ± 10.3[*14]	7.08 (2.83, 67.2)	7.49 ± 1.90[*18]

Mean ± standard deviation (individual values for N = 1 or 2); "—," not calculated; *1, ng/mL (for DXd); *2, ng·day/mL (for DXd); *3, median (Min, Max); *4, PK parameters for Cycle 3, Day 1 were not calculated; *5, N = 47; *6, N = 49; *7, N = 48; *8, N = 73; *9, N = 3; *10, N = 43; *11, N = 45; *12, N = 44; *13, N = 72; *14, N = 30; *15, N = 29; *16, N = 31; *17, N = 24; *18, N = 27

10) The ratio of AUC_{21day} on Cycle 3, Day 1 to AUC_{21day} on Cycle 1, Day 1

6.2.1.2 Global phase I study (CTD 5.3.3.2-2, Study TP01 [Breast cancer cohort, ongoing since [redacted] 20[redacted], data cut-off on [redacted] [redacted], 20[redacted]])

An open-label uncontrolled study was conducted to investigate the PK and other aspects of datopotamab deruxtecan in 85 patients (N = 85 for PK analysis) with unresectable or recurrent (1) HR-negative, HER2-negative breast cancer or (2) HR-positive, HER2-negative breast cancer for which no standard treatment was available. Datopotamab deruxtecan 6.0 or 8.0 mg/kg was administered to the patients in the above category (1) and 6.0 mg/kg to patients in (2), every 3 weeks intravenously in 3-week cycles. Plasma datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd concentrations were evaluated.

The PK parameters for datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd in patients in (1) and (2) are presented in Table 17 and Table 18, respectively.

Table 17. Pharmacokinetic parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd ([1] patients with HR-negative, HER2-negative breast cancer)

Dosing day	Analyte	Dose (mg/kg)	N	C_{max} (μg/mL[*1])	AUC_{21day} (μg·day/mL[*2])	t_{max}[*3] (h)	$t_{1/2}$ (day)
Cycle 1, Day 1	Datopotamab deruxtecan	6.0	41	166 ± 32.4	765 ± 177[*4]	2.00 (1.50, 22.1)	5.04 ± 0.845[*4]
		8.0	2	182, 242	431, 991	3.12, 4.80	3.06, 4.42
	Total anti-TROP-2 antibody	6.0	41	168 ± 29.0	787 ± 179[*4]	1.98 (1.50, 22.1)	5.62 ± 1.10[*4]
		8.0	2	174, 220	435, 1,010	3.12, 4.80	3.26, 4.85
	DXd	6.0	42	3.06 ± 2.99	21.1 ± 17.3[*4]	22.1 (3.13, 94.8)	5.97 ± 1.14[*4]
		8.0	2	3.75, 5.02	21.3, 31.4	6.87, 6.88	4.25, 4.97
Cycle 3, Day 1	Datopotamab deruxtecan	6.0	17	176 ± 24.7	957 ± 178	2.93 (0.567, 7.17)	5.66 ± 0.692
		8.0	2	136, 265	461, 1,370	3.07, 3.12	3.50, 5.56
	Total anti-TROP-2 antibody	6.0	17	178 ± 26.8	1,030 ± 208	1.70 (0.500, 7.17)	6.12 ± 0.997
		8.0	2	150, 244	527, 1,350	3.07, 3.12	3.91, 6.32
	DXd	6.0	17	2.73 ± 1.13	20.0 ± 6.02[*5]	7.08 (4.32, 69.6)	7.41 ± 1.41[*5]
		8.0	2	3.07, 4.63	20.7, 31.5	7.10, 48.5	7.60

Mean ± standard deviation (individual values for N = 1 or 2); *1, ng/mL (for DXd); *2, ng·day/mL (for DXd); *3, median (Min, Max); *4, N = 40; *5, N = 15

Table 18. Pharmacokinetic parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd ([2] patients with HR-positive, HER2-negative breast cancer)

Dosing day[*1]	Analyte	N	C_{max} (μg/mL[*2])	AUC_{21day} (μg·day/mL[*3])	t_{max}[*4] (h)	$t_{1/2}$ (day)
Cycle 1, Day 1	Datopotamab deruxtecan	41	172 ± 28.6	796 ± 203	1.97 (1.62, 5.02)	4.93 ± 1.35
	Total anti-TROP-2 antibody	41	172 ± 29.5	821 ± 220	1.92 (1.50, 5.03)	5.26 ± 1.62
	DXd	41	4.71 ± 9.97	22.3 ± 10.1[*5]	22.1 (2.83, 193)	5.83 ± 1.15[*6]

Mean ± standard deviation; *1, PK parameters for Cycle 3, Day 1 were not calculated; *2, ng/mL (for DXd); *3, ng·day/mL (for DXd); *4, median (Min, Max); *5, N = 37; *6, N = 36

6.2.2 Relationship between exposure and change in QT/QTc interval

The relationships between plasma datopotamab deruxtecan and DXd concentrations and change from baseline in QT interval corrected with Fridericia's formula (ΔQTcF) were investigated using a linear mixed effects model based on data from 195 subjects enrolled in the global phase I study (Study TP01) whose plasma datopotamab deruxtecan and DXd concentrations and electrocardiographic measurements were able to be taken at the same time. There was no clear relationship of plasma datopotamab deruxtecan and DXd concentrations with ΔQTcF. It was estimated that following intravenous administration of datopotamab deruxtecan 8.0 mg/kg every 3 weeks, the upper bound of the 90% CI for ΔQTcF at C_{max}

of datopotamab deruxtecan and DXd (201 μg/mL and 3.51 ng/mL) in Cycle 1 or Cycle 3 was 2.18 and 1.12 milliseconds, respectively.

On the basis of the above, the applicant explained that datopotamab deruxtecan is unlikely to cause QT/QTc interval prolongation when used according to the proposed dosage regimen.

6.2.3 Population pharmacokinetic analyses

Population pharmacokinetic (PPK) analyses were performed based on the PK data of datopotamab deruxtecan and DXd (N = 1,081; 11,735 timepoints for datopotamab deruxtecan and 11,723 timepoints for DXd)[11)] from the global phase I study (Study TP01), global phase II study (Study TL05), and global phase III studies (Studies TL01 and TB01) using a non-linear mixed effects model (software, NONMEM Version 7.3.0). The PK for datopotamab deruxtecan was described by a two-compartment model with linear and non-linear Michaelis-Menten type elimination processes, while the PK for DXd was described by a one-compartment model with a time-changing DXd generation from datopotamab deruxtecan and first-order elimination processes.

Table 19 shows the PK parameters and covariates studied in the analyses.

Table 19. Covariates studied

Analyte	PK parameter	Covariates
Datopotamab deruxtecan	CL_{lin}	Body weight, albumin, CrCL, age, sex, country of enrollment (Japan, other countries), formulation, anti-Dato-DXd antibody expression status, cancer type (NSCLC, HR-negative, HER2-negative breast cancer, HR-positive, HER2-negative breast cancer, other), and geographical region (East Asia, non-East Asia, other)
	Vc	Body weight and sex
	Vp	Body weight
	V_{max}	Tumor size
DXd	CL	Body weight, albumin, total bilirubin, AST, CrCL, country of enrollment (Japan, US, Europe, other countries), formulation, cancer type (NSCLC, HR-negative, HER2-negative breast cancer, HR-positive, HER2-negative breast cancer, other), and geographical region (East Asia, non-East Asia, other)
	Vc	Body weight and sex

The following covariates were identified for datopotamab deruxtecan: body weight, albumin, age, sex, and country of enrollment (Japan, other countries) on linear clearance (CL_{lin}); body weight and sex on volume of distribution of central compartment (Vc); body weight on volume of distribution of peripheral compartment (Vp); and tumor size on maximum elimination rate (V_{max}). The following covariates were identified for DXd: body weight, albumin, total bilirubin, aspartate aminotransferase (AST), and country of enrollment (Japan, US,

11) Of patients who were subjected to analyses, the median (Min, Max) for patient characteristic values, or the number of patients classified in each category are as follows:
Body weight, 64.2 kg (35.6, 156); albumin, 39.0 g/L (19.0, 75.4); total bilirubin, 0.400 mg/dL (0.0900, 3.32); AST, 25.0 U/L (5.00, 239); CrCL, 85.4 mL/min (24.6, 150); tumor size, 60.0 mm (10.0, 341); age, 60 years (26, 86); sex, 355 males, 726 females; country of enrollment, 192 patients (Japan), 321 patients (US), 301 patients (Europe), 267 patients (other); formulation, 295 patients (liquid for clinical study), 446 patients (lyophilized powder for clinical study), 145 patients (to-be-marketed), 194 patients (lyophilized powder for clinical study and to-be-marketed), 1 patient (unknown); anti-Dato-DXd antibodies, 163 patients (positive), 908 patients (negative), 10 patients (unknown); cancer type, 643 patients (NSCLC), 44 patients (HR-negative, HER2-negative breast cancer), 393 patients (HR-positive, HER2-negative breast cancer), 1 patient (other); geographical region, 384 patients (East Asia), 7 patients (non-East Asia), and 690 patients (other)

Europe, other countries) on total body clearance (CL); and body weight and sex on Vc. The applicant's explanation about the results:

- The steady-state AUC ratio of the 5th percentile to median body weight and that of the 95th percentile to median body weight was estimated to be 0.79 and 1.25, respectively for datopotamab deruxtecan, and 0.77 and 1.39, respectively, for DXd. Although datopotamab deruxtecan and DXd exposures increased with increase in body weight, given that the exposure ranges for body weight categories roughly overlapped to each other, as well as other factors, body weight is unlikely to have effects on the PK of datopotamab deruxtecan and DXd that lead to clinical problems.
- The effects of albumin, tumor size, age, sex, and country of enrollment on datopotamab deruxtecan exposure, and the effects of albumin, total bilirubin, AST, sex, and country of enrollment on DXd exposure were not significant [12)]; therefore, these covariates are unlikely to have effects on the PK of datopotamab deruxtecan and DXd that lead to clinical problems.

6.2.4 Exposure-efficacy/safety relationship

6.2.4.1 Exposure-efficacy relationship

Based on the results of the global phase III study (Study TB01), the relationships between datopotamab deruxtecan exposure [13)] (AUC in Cycle 1) and overall survival (OS) and between datopotamab deruxtecan exposure[13)] (C_{avg}[14)] and AUC in Cycle 1) and progression free survival (PFS) and objective response rate were investigated. The results showed that OS tended to increase with increase in datopotamab deruxtecan exposure. Conversely, there was no clear relationship between datopotamab deruxtecan exposure and PFS or objective response rate.

6.2.4.2 Exposure-safety relationship

Based on the results of the global phase I study (Study TP01), global phase II study (Study TL05), and global phase III studies (Studies TL01 and TB01), the relationships between datopotamab deruxtecan and DXd exposures[13)] (C_{avg}[14)] and AUC and C_{max} in Cycle 1) and the following events were investigated: Grade ≥3 adverse events, serious adverse events, adverse events leading to infusion interruption of datopotamab deruxtecan, adverse events leading to dose reduction of datopotamab deruxtecan, adverse events leading to treatment discontinuation of datopotamab deruxtecan, stomatitis-related adverse events of

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12) The AUC ratios at steady state for datopotamab deruxtecan and DXd were as follows:
- The AUC ratio of the 5th percentile to median albumin and that of the 95th percentile to median albumin were 0.85 and 1.10, respectively (datopotamab deruxtecan) and 1.16 and 0.92, respectively (DXd)
- The AUC ratio of the 5th percentile to median tumor size and that of the 95th percentile to median tumor size were 1.05 and 0.96, respectively (datopotamab deruxtecan)
- The AUC ratio of the 5th percentile to median age and that of the 95th percentile to median age were 0.88 and 1.07, respectively (datopotamab deruxtecan)
- The AUC ratio of male patients compared to female patients was 0.84 for datopotamab deruxtecan and 1.01 for DXd
- By country of enrollment, the AUC ratio for Japan relative to that for the US was 1.20 (datopotamab deruxtecan) and 0.98 (DXd), Europe relative to the US was 0.79 (DXd), and other countries relative to the US was 0.89 (DXd)
- The AUC ratio of the 5th percentile to median total bilirubin and that of the 95th percentile to median total bilirubin were 0.90 and 1.16, respectively (DXd)
- The AUC ratio of the 5th percentile to median AST and that of the 95th percentile to median AST were 0.90 and 1.23, respectively (DXd)

13) Estimated by the PPK analysis [see Section 6.2.3].

14) The average concentration for the time period from the onset day of the event to the end of the cycle

any grade and Grade ≥2, eye disorder-related adverse events of any grade and Grade ≥2, events determined to be datopotamab deruxtecan-associated interstitial lung disease (ILD) by the independent review board for ILD. The following relationships were detected between datopotamab deruxtecan or DXd exposure and adverse events.

- The incidences of adverse events leading to interruption or dose reduction of datopotamab deruxtecan and Grade ≥2 stomatitis-related adverse events tended to increase with increased datopotamab deruxtecan AUC in Cycle 1.
- The incidences of stomatitis-related adverse events of any grade, eye disorder-related adverse events of any grade, and Grade ≥2 adverse events tended to increase with increased datopotamab deruxtecan C_{avg}.
- The incidences of Grade ≥3 adverse events and serious adverse events tended to increase with increased DXd C_{avg}.

No clear relationship was observed between the incidences of adverse events leading to discontinuation of datopotamab deruxtecan or datopotamab deruxtecan-associated ILD determined by the independent review board for ILD and exposures to datopotamab deruxtecan and DXd.

6.2.5 Effects of impaired renal function on PK

No clinical studies have been conducted to evaluate the effects of renal impairment on the PK of datopotamab deruxtecan in patients with renal impairment.

The applicant explained that taking into account the factors below, deteriorated renal function is unlikely to affect the PK of datopotamab deruxtecan and DXd.

- Since datopotamab deruxtecan is thought to be eliminated through a degradation pathway mediated by target antigen binding and a nonspecific protein degradation pathway, impairment of renal function is unlikely to affect exposure to datopotamab deruxtecan.
- In the PPK analyses, creatinine clearance (CrCL) was not identified as a significant covariate for any PK parameters of datopotamab deruxtecan or DXd [see Section 6.2.3].
- In the PPK analyses [see Section 6.2.3], DXd exposure was estimated for each of the renal function categories[15)]: patients with normal renal function (N = 464), mild renal impairment (N = 439), moderate renal impairment (N = 176), and severe renal impairment (N = 2). The dose-corrected, impaired-to-normal AUC ratio for DXd in Cycle 3 was 0.87 (mild), 0.90 (moderate), and 0.76 (severe).

6.2.6 Differences in PK of datopotamab deruxtecan between Japanese and non-Japanese populations

The applicant explained that taking into account the factors below, there are no clear differences in the PK of datopotamab deruxtecan or DXd between Japanese and non-Japanese populations.

- Table 20 shows the PK parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd following intravenous administration of datopotamab deruxtecan 6.0 mg/kg in Cycle 1 in the global phase

15) Patients were classified based on CrCL measurements: normal renal function, ≥90 mL/min; mild renal impairment, ≥60 to <90 mL/min; moderate renal impairment, ≥30 to <60 mL/min; and severe renal impairment, ≥15 to <30 mL/min.

I study (Study TP01), global phase II study (Study TL05), and global phase III study (Study TL01). No clear differences were found between Japanese and non-Japanese patients.

- In the PPK analyses, country of enrollment was identified as a significant covariate for CL_{lin} of datopotamab deruxtecan and CL of DXd [see Section 6.2.3]. However, the geometric mean ratio of non-Japanese to Japanese patients for steady state C_{max} was 1.11 (datopotamab deruxtecan) and 1.06 (DXd), and that for steady state AUC was 0.96 (datopotamab deruxtecan) and 1.00 (DXd), suggesting no clear differences between Japanese and non-Japanese patients.

Table 20. Pharmacokinetic parameters of datopotamab deruxtecan, total anti-TROP-2 antibody, and DXd

Analyte	Patient population	N	C_{max} (μg/mL*2)	N	t_{max}*1 (h)	N	AUC_{21day} (μg·day/mL*3)	N	$t_{1/2}$ (day)
Datopotamab deruxtecan	Japanese	47	158 ± 26	47	2.02 (1.55, 22.1)	45	709 ± 164	45	4.89 ± 0.960
	Non-Japanese	150	156 ± 33.4	150	2.02 (1.50, 192)	148	700 ± 237	147	4.85 ± 1.10
Total anti-TROP-2 antibody	Japanese	47	157 ± 28.2	47	2.02 (1.55, 22.1)	46	735 ± 184	46	5.29 ± 1.25
	Non-Japanese	150	157 ± 33.4	150	2.00 (1.50, 192)	149	737 ± 242	148	5.24 ± 1.30
DXd	Japanese	47	3.35 ± 2.63	47	7.00 (3.00, 70.3)	45	21.4 ± 17.5	45	5.73 ± 0.98
	Non-Japanese	151	3.58 ± 5.61	151	22.4 (2.78, 193)	138	20.2 ± 11.8	134	5.52 ± 1.06

Mean ± standard deviation; *1, median (Min, Max); *2, ng/mL (for DXd); *3, ng·day/mL (for DXd)

6.2.7 Effects of anti-Dato-DXd antibodies on the PK of datopotamab deruxtecan

The incidence of anti-Dato-DXd antibodies was investigated in the breast cancer cohort of the global phase I study (Study TP01) and the global phase III study (Study TB01). In patients treated with intravenous datopotamab deruxtecan 6.0 mg/kg in either study and evaluated for anti-Dato-DXd antibodies and neutralizing antibodies to datopotamab deruxtecan, anti-Dato-DXd antibodies were detected in 60[16)] of 435 patients (13.8%) and neutralizing antibodies in 9 of 435 patients (2.1%).

The applicant's explanation about the effects of datopotamab deruxtecan in the sample on the measurement of anti-Dato-DXd antibodies:

The upper limits of datopotamab deruxtecan concentrations that will not affect the measurement of anti-Dato-DXd antibodies by the assay method used for the measurement in Studies TP01 and TB01 [see Section 6.1] were 50 and 25 μg/mL, respectively. In these studies, datopotamab deruxtecan concentrations in samples at the time of measurement were at or lower than the upper limits shown above in 1,168 of 1,181 samples. It is thus unlikely that datopotamab deruxtecan in samples affected anti-Dato-DXd antibody measurement.

The applicant's explanation about the effects of anti-Dato-DXd antibodies on the PK of datopotamab deruxtecan:

Table 21 shows plasma datopotamab deruxtecan concentrations of patients in the Study TP01 breast cancer cohort and Study TB01 who were treated with intravenous datopotamab deruxtecan 6.0 mg/kg with evaluable datopotamab deruxtecan PK at the time of the anti-Dato-DXd antibody measurement. There were no clear differences in plasma datopotamab deruxtecan concentrations between anti-Dato-DXd antibody-positive

16) Including 4 subjects who were anti-Dato-DXd antibody-positive at baseline and had 4-fold increase in anti-Dato-DXd antibody titer from baseline after the administration of datopotamab deruxtecan.

and -negative patients. Based on the results, etc., it is unlikely that anti-Dato-DXd antibodies will affect the PK of datopotamab deruxtecan.

Table 21. Plasma datopotamab deruxtecan concentrations in anti-Dato-DXd antibody-positive and -negative patients

Study	Dosing day	Anti-Dato-DXd antibody-positive patients		Anti-Dato-DXd antibody-negative patients	
		N	Pre-dosing concentration (μg/mL)	N	Pre-dosing concentration (μg/mL)
TP01	Cycle 2, Day 1	6	3.5 (150)	74	4.4 (113)
	Cycle 4, Day 1	5	5.1 (87.2)	58	7.9 (94.2)
	Cycle 6, Day 1	3	3.9 (567)	46	7.9 (105)
	Cycle 8, Day 1	1	15.8	32	7.6 (84.0)
TB01	Cycle 2, Day 1	36	2.09 (134)	166	2.60 (127)
	Cycle 4, Day 1	27	4.48 (132)	128	4.61 (99.7)
	Cycle 6, Day 1	21	6.56 (208)	99	5.41 (146)
	Cycle 8, Day 1	12	8.04 (77.0)	58	5.41 (98.6)

Geometric mean (geometric coefficient of variation, %) (individual value for N = 1)

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation regarding clinical pharmacology of datopotamab deruxtecan was acceptable except for the issues discussed in the following sections.

6.R.1 Use of datopotamab deruxtecan in patients with hepatic impairment

No clinical studies have been conducted in patients with hepatic impairment to evaluate the effects of hepatic impairment on the PK of datopotamab deruxtecan.

The applicant's explanation about the use of datopotamab deruxtecan in patients with hepatic impairment:
Taking into account the factors below, no adjustment to the dose of datopotamab deruxtecan is necessary for patients with mild and moderate hepatic impairment.

- Using the PPK analyses [see Section 6.2.3], DXd exposure was estimated for each of the hepatic function categories[17]: patients with normal hepatic function (N = 779), mild hepatic impairment (N = 295), and moderate hepatic impairment (N = 6). The dose-corrected, impaired-to-normal C_{max} ratio for DXd in Cycle 3 was 1.19 (mild) and 2.51 (moderate), and the dose-corrected, impaired-to-normal AUC ratio for DXd in Cycle 3 was 1.14 (mild) and 2.40 (moderate). There was no increase in DXd exposure in patients with mild hepatic impairment. In patients with moderate hepatic impairment, there was an increase in DXd exposure; however, because the number of patients with moderate impairment was small, it is difficult to draw a definite conclusion on the effect of moderate hepatic impairment on the PK of datopotamab deruxtecan.
- Based on the results from the breast cancer cohort of the global phase I study (Study TP01) and the global phase III study (Study TB01), the incidences of adverse events in patients with normal hepatic function[17] (N = 234), mild hepatic impairment (N = 202), and moderate hepatic impairment (N = 6) were as follows: adverse events resulting in death, 0.4% (normal), 0% (mild), and 0% (moderate); serious

[17] The hepatic function status was classified according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

adverse events, 12.8% (normal), 18.3% (mild), and 0% (moderate); adverse events leading to treatment discontinuation, 3.4% (normal), 4.0% (mild), and 16.7% (moderate); adverse events leading to dose interruption, 24.4% (normal), 23.3% (mild), and 0% (moderate); adverse events leading to dose reduction, 21.8% (normal), 20.3% (mild), and 16.7% (moderate). The results indicate that there were no trends towards an increase in the incidence of adverse events in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function.

Patients with severe hepatic impairment were excluded from Study TB01. Given that biliary excretion or hepatic metabolism is involved in the elimination of DXd [see Sections 4.3.2 and 4.4.1], the package insert will caution about potential increase in blood DXd concentration due to hepatic impairment, with a note that no clinical studies have been conducted in patients with severe hepatic impairment.

PMDA's view:
The applicant's explanation about the use of datopotamab deruxtecan in patients with mild and severe hepatic impairment is acceptable.

Although only a small number of patients with moderate hepatic impairment received datopotamab deruxtecan, DXd exposure increased in these patients compared to those with normal hepatic function. The package insert should caution about possible increase in blood DXd concentration in patients with moderate or severe hepatic impairment.

Also, healthcare professionals should always be updated with new findings on the PK of datopotamab deruxtecan and DXd from patients with hepatic impairment in an appropriate manner.

6.R.2 Pharmacokinetic drug interactions with CYP3A, P-gp, BCRP, and OATP1B inhibitors

The applicant's explanation about the coadministration of datopotamab deruxtecan with CYP3A, P-gp, BCRP, and OATP1B inhibitors:
DXd is a substrate of CYP3A, P-gp, BCRP, OATP1B1, and OATP1B3 [see Sections 4.3.2 and 4.5.3]. The effects of itraconazole (strong CYP3A inhibitor and P-gp and BCRP inhibitor) (*J Pharm Sci*. 2007;96:3226-35) and ritonavir (strong CYP3A inhibitor and P-gp, BCRP,[18)] and OATP1B inhibitor) (*J Pharmacol Exp Ther*. 2004;310:334-41) on the PK of DXd were investigated using the physiologically based pharmacokinetics (PBPK) model.[19)] The estimated values obtained from the PBPK model were generally in agreement with the results below; therefore, the model is appropriate.

[18)] Because a preliminary PBPK model analysis suggested that ritonavir is a weak inhibitor of BCRP, BCRP inhibition-related parameters for ritonavir were not defined.

[19)] For the PBPK model analysis, Simcyp version 21 was used. The minimal PBPK model (datopotamab deruxtecan) and the full PBPK model (DXd) were selected. A 94.9% contribution of CYP3A to DXd metabolism was assumed based on the results of an *in vitro* study [see Section 4.3.2]. In addition, based on the results of *in vitro* studies, the effects of OATP1B1 and OATP1B3 on hepatic uptake of DXd and the effects of P-gp and BCRP on DXd elimination were incorporated. The default values of Simcyp were used for physiological parameters and itraconazole-related parameters, while parameters related to inhibition of OATP1B1 and OATP1B3 by ritonavir were defined based on values from a published paper (*Drug Metab Dispos.* 2017;45:755-764).

- The DXd exposure and plasma concentrations over time obtained from Study J101, a global phase I study of T-DXd in patients with unresectable or recurrent HER2-positive breast cancer, etc. (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020)
- The DXd exposure and plasma concentrations over time obtained from the global phase I study (Study TP01)
- The measured DXd exposure ratio of coadministration with itraconazole to T-DXd alone, and that of coadministration of ritonavir to T-DXd alone (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020)

The results showed that in healthy Japanese adults, the DXd exposure geometric mean ratio of coadministration with itraconazole to datopotamab deruxtecan alone was 1.20 (C_{max}) and 1.20 (AUC), and that of coadministration with ritonavir to datopotamab deruxtecan alone was 1.26 (C_{max}) and 1.24 (AUC). In White patients with cancer, the DXd exposure geometric mean ratio of coadministration with itraconazole to datopotamab deruxtecan alone was 1.21 (C_{max}) and 1.21 (AUC), and that of coadministration with ritonavir to datopotamab deruxtecan alone was 1.34 (C_{max}) and 1.32 (AUC). Based on the above, like T-DXd, datopotamab deruxtecan is also unlikely to have a clinically significant impact on DXd exposure when coadministered with CYP3A, P-gp, BCRP, or OATP1B inhibitor drugs. Cautioning in the package insert about coadministration with CYP3A, P-gp, BCRP, and OATP1B inhibitors is unnecessary.

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data of datopotamab deruxtecan in the form of results data from studies as summarized in Table 22.

Table 22. List of clinical studies on efficacy and safety

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Global	TP01	I	**Dose escalation part** NSCLC cohort: Patients with unresectable advanced/recurrent NSCLC for which no standard treatment is available Breast cancer cohort: Patients with unresectable or recurrent HR-negative, HER2-negative breast cancer for which no standard treatment is available	173	NSCLC cohort: Datopotamab deruxtecan 0.27, 0.5, 1, 2, 4, 6, 8, or 10 mg/kg intravenously Q3W Breast cancer cohort: Datopotamab deruxtecan 6 or 8 mg/kg intravenously Q3W	Tolerability Safety PK
				Dose expansion part NSCLC cohort: Patients with unresectable advanced/recurrent NSCLC for which no standard treatment is available Breast cancer cohort: Patients with unresectable or recurrent HR-positive, HER2-negative breast cancer for which no standard treatment is available	122	NSCLC cohort: Datopotamab deruxtecan 4, 6, or 8 mg/kg intravenously Q3W Breast cancer cohort: Datopotamab deruxtecan 6 mg/kg intravenously Q3W	
		TB01	III	Patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy	Arm 1: 365 Arm 2: 367	Arm 1: Datopotamab deruxtecan 6 mg/kg intravenously Q3W Arm 2: ICC*	Efficacy Safety

*, One agent was to be selected by the investigator from the following options: eribulin, capecitabine, gemcitabine, or vinorelbine (see Table 23 for the dosage regimens)

The following sections summarize the clinical studies. Main adverse events other than deaths that occurred in the clinical studies are described in Section "7.2 Adverse events and other findings observed in clinical studies."

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase I studies (CTD 5.3.3.2-1, Study TP01, NSCLC cohort [ongoing since February 2018, data cut-off on [redacted], 20[redacted]]; CTD 5.3.3.2-2, Study TP01, Breast cancer cohort [ongoing since [redacted] 20[redacted], data cut-off on [redacted], 20[redacted]]

An open-label, uncontrolled study was conducted in Japan and the US (13 study centers for the NSCLC cohort and 12 study centers for the breast cancer cohort) to investigate the tolerability, safety, PK, and other aspects of datopotamab deruxtecan in patients who met the criteria in the table below. The patients were to receive the dosage regimens in the table, and treatment was to be continued until disease progression or treatment discontinuation criteria were met.

		NSCLC cohort	Breast cancer cohort
Dose escalation part	Study population	Patients with unresectable advanced/recurrent NSCLC for which no standard treatment is available	Patients with unresectable or recurrent HR-negative, HER2-negative[*2] breast cancer for which no standard treatment is available
	Target sample size	Total of all dose groups at or less than MTD, up to 40 subjects	Total of all dose groups at or less than MTD, up to 40 subjects
	Dosage regimen	Datopotamab deruxtecan 0.27, 0.5, 1, 2, 4, 6, 8, or 10 mg/kg intravenously[*1] Q3W	Datopotamab deruxtecan 6 or 8 mg/kg intravenously[*1] Q3W
Dose expansion part	Study population	Patients with unresectable advanced/recurrent NSCLC for which no standard treatment is available	• Patients with unresectable or recurrent HR-negative, HER2-negative[*2] breast cancer for which no standard treatment is available • Patients with unresectable or recurrent HR-positive, HER2-negative[*2] breast cancer for which no standard treatment is available[*3]
	Target sample size	40 subjects for each dose group	40 subjects for each study population
	Dosage regimen	Datopotamab deruxtecan 4, 6, or 8 mg/kg intravenously[*1] Q3W	Datopotamab deruxtecan 6 mg/kg intravenously[*1] Q3W

*1, The first dose was to be administered over approximately 90 minutes. If the first infusion was tolerated, the second and subsequent infusions may be administered over a period of approximately 30 minutes; *2, HR-positive is defined as ≥1% estrogen receptor or progesterone receptor-positivity, HR-negative is defined as <1% estrogen receptor or progesterone receptor-positivity; HER2-negative (defined as IHC 0, IHC 1+, or IHC 2+/ISH−); HR and HER2 statuses were to be determined by the study site; *3, eligible patients were those with endocrine therapy resistance (advanced after one or more lines of endocrine therapy, and endocrine therapy was no longer effective for the patient as assessed by the investigator) and unresectable or recurrent breast cancer who had received 1 to 3 prior lines of chemotherapy.

All 210 subjects enrolled in the NSCLC cohort of the study (129 subjects in the dose escalation part and 81 subjects in the dose expansion part) and all 85 subjects enrolled in the breast cancer cohort (44 subjects in the dose escalation part and 41 subjects in the dose expansion part[20)]) received datopotamab deruxtecan, and were included in the safety analysis set, including 59 Japanese subjects in the NSCLC cohort (29 subjects in the dose escalation part and 30 subjects in the dose expansion part) and 19 subjects in the breast cancer cohort (13 subjects in the dose escalation part and 6 subjects in the dose expansion part).

In the dose escalation part of the NSCLC cohort in this study, the first 21 days of datopotamab deruxtecan treatment were defined as the dose-limiting toxicity (DLT) assessment period. Of the subjects enrolled in the study before the maximum tolerated dose (MTD) was determined, 1 subject in the 10 mg group in the dose escalation part was excluded, and the remaining 51 subjects were analyzed for DLT. Dose-limiting toxicities were reported in 1 of 8 subjects in the 6 mg/kg group (Grade 3 rash maculo-papular) and 2 of 7 subjects in the 10 mg/kg group (Grade 3 stomatitis and Grade 3 mucosal inflammation in 1 subject each). Therefore, the MTD for datopotamab deruxtecan was determined to be 8 mg/kg every 3 weeks. Later, the recommended phase 2 dose (RP2D) for datopotamab deruxtecan was established as 6 mg/kg every 3 weeks based on the safety and efficacy results, etc. obtained in the dose escalation and dose expansion parts of the study.

In the dose escalation and dose expansion parts of the study, deaths during treatment or within 35 days from the last dose of datopotamab deruxtecan were reported as follows. (None of the Japanese patients died):

20) The evaluation of HR-negative patients had been completed in the dose escalation part; therefore, only HR-positive patients were enrolled in the dose expansion part.

(1) Dose escalation part:

In the NSCLC cohort, 1 of 4 subjects (25.0%) died in the 0.27 mg/kg group, 1 of 5 subjects (20.0%) in the 0.5 mg/kg group, 0 of 7 subjects in the 1 mg/kg group, 1 of 6 subjects (16.7%) in the 2 mg/kg group, 3 of 29 subjects (10.3%) in the 4 mg/kg group, 4 of 34 subjects (11.8%) in the 6 mg/kg group, 4 of 36 subjects (11.1%) in the 8 mg/kg group, and 1 of 8 subjects (12.5%) in the 10 mg/kg group. There were no deaths in the breast cancer cohort. In the NSCLC cohort, deaths due to disease progression were as follows: 1 subject in the 0.27 mg/kg group, 1 subject in the 0.5 mg/kg group, 1 subject in the 2 mg/kg group, 1 subject in the 4 mg/kg group, 2 subjects in the 6 mg/kg group, 1 subject in the 8 mg/kg group, and 1 subject in the 10 mg/kg group. Other causes of death were pulmonary embolism and respiratory failure (1 subject each) in the 4 mg group; respiratory failure and cardiomyopathy/pneumonitis (1 subject each) in the 6 mg group; respiratory tract infection, sepsis, and pneumonitis (1 subject each) in the 8 mg group. Among these events, a causal relationship to datopotamab deruxtecan could not be ruled out for respiratory failure (1 subject) in the 4 mg group, pneumonitis (1 subject) in the 6 mg group, and pneumonitis (1 subject) in the 8 mg group.

(2) Dose expansion part:

In the NSCLC cohort, 0 of 21 subjects died in the 4 mg/kg group, 3 of 16 subjects (18.8%) in the 6 mg/kg group, and 4 of 44 subjects (9.1%) in the 8 mg/kg group. In the breast cancer cohort, 2 of 41 subjects (4.9%) died. Three subjects in the 8 mg/kg group in the NSCLC cohort and 1 subject in the breast cancer cohort died due to disease progression. Other causes of death were neck pain, unknown, and other (death) (1 subject each) in the 6 mg group and dyspnoea/pneumonitis (1 subject) in the 8 mg group in the NSCLC cohort; dyspnoea (1 subject) in the breast cancer cohort. Among these events, in terms of cause of death due to adverse events,[21)] a causal relationship to datopotamab deruxtecan could not be ruled out for dyspnoea/pneumonitis (1 subject) in the 8 mg group in the NSCLC cohort.

7.1.1.2 Global phase III study (CTD 5.3.5.1-1, Study TB01 [ongoing since October 2021, data cut-off on July 17, 2023])

A randomized, open-label study was conducted at 166 study centers in 20 countries and regions including Japan in patients with unresectable or recurrent HR-positive, HER2-negative[22)] breast cancer who had received prior chemotherapy[23)] (target sample size, approximately 700 subjects[24)]) to evaluate the efficacy and safety of datopotamab deruxtecan versus investigator's choice chemotherapy (ICC).

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21) The causes of death were classified into "adverse events," "disease progression," "other," and "unknown." Causes classified as "adverse events" were assessed to ascertain if there was a causal relationship to datopotamab deruxtecan.

22) HR-positive is defined as ≥1% estrogen receptor or progesterone receptor-positivity, HER2-negative is defined as IHC 0, IHC 1+, or IHC 2+/ISH−, and HR and HER2 statuses were to be determined by the study site.

23) Patients who met both of the following criteria were eligible.
- Patients who have progressed on endocrine therapy or are ineligible for endocrine therapy, per investigator assessment
- Patients with unresectable or recurrent breast cancer who had received 1 or 2 prior lines of chemotherapy

24) The primary endpoints were PFS as assessed by blinded independent central review (BICR) and OS. Assuming a randomization ratio (datopotamab deruxtecan to ICC) of 1:1, a hazard ratio (datopotamab deruxtecan to ICC) of 0.55 (PFS) and 0.75 (OS), two-sided significance level of 0.01 (PFS), and 0.04 (OS), 419 PFS events and 444 OS events would provide statistical power of >99% (PFS) and 83% (OS). Taking into account the follow-up period, etc. a sample size of approximately 700 subjects was selected. The upper limits of patients who had received 2 lines of prior chemotherapy for unresectable or recurrent breast cancer and patients with no prior cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors were 50% and 49%, respectively.

Subjects were to receive datopotamab deruxtecan 6 mg/kg intravenously[25)] every 3 weeks, each cycle consisting of 3 weeks in the datopotamab deruxtecan group. In the ICC group, one agent was to be selected by the investigator from the options listed in Table 23, and treatment was to be continued until disease progression or treatment discontinuation criteria were met.

Table 23. The dosage regimen for optional agents listed for the ICC group in Study TB01

Agent	Dosage regimen
Eribulin	1.4 mg/m^2 IV on Days 1 and 8
Capecitabine	1,000 or 1,250 mg/m^2 from Day 1 to Day 14 orally BID
Gemcitabine	1,000 mg/m^2 IV on Days 1 and 8
Vinorelbine	25 mg/m^2 IV on Days 1 and 8

All 732 subjects enrolled in the study and randomized (365 subjects in the datopotamab deruxtecan group and 367 subjects in the ICC group) were included in the full analysis set (FAS) and were analyzed for efficacy (including 32 Japanese subjects in the datopotamab deruxtecan group and 38 Japanese subjects in the ICC group). Of the FAS, 21 subjects who did not receive the study drug were excluded, and the remaining 711 subjects (360 subjects in the datopotamab deruxtecan group and 351 subjects in the ICC group) were included in the safety analysis set (including 31 Japanese subjects in the datopotamab deruxtecan group and 38 Japanese subjects in the ICC group).

The primary endpoints were PFS assessed by BICR according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 and OS. The efficacy of datopotamab deruxtecan was considered to have been demonstrated when statistically significant prolongation was achieved in either PFS or OS. To adjust multiplicity associated with multiple primary endpoints, two-sided significance levels, 0.01 for PFS and 0.04 for OS, were used, and if a statistically significant prolongation was observed in PFS, the OS analysis was to be performed with a two-sided significance level of 0.05 so that type I error for the total study would be 0.05 (two-sided).

The primary PFS analysis was scheduled to be performed when approximately 419 PFS events had occurred. OS analysis was scheduled with (1) the first interim analysis at the time of the primary PFS analysis, the second interim analysis when approximately 355 OS events had occurred, and the final analysis with approximately 444 OS events. The O'Brien and Fleming spending α function based on the Lan-DeMets approach was to be used to control type I error associated with the OS interim analysis.

The results of the primary analysis of PFS assessed by BICR, one of the primary endpoints (data cut-off on July 17, 2023) and the Kaplan-Meier plot are shown in Table 24 and Figure 2, respectively. The results demonstrated the superiority of datopotamab deruxtecan over ICC.

[25)] The first dose was to be administered over approximately 90 minutes. If the first infusion was tolerated, the subsequent infusions may be administered over approximately 30 minutes.

Table 24. The primary analysis results of PFS (FAS, BICR assessment, data cut-off on July 17, 2023)

	Datopotamab deruxtecan		ICC
Number of subjects	365		367
Number of events (%)	212 (58.1)		235 (64.0)
Median [95% CI] (months)	6.9 [5.7, 7.4]		4.9 [4.2, 5.5]
Hazard ratio [95% CI]*1		0.63 [0.52, 0.76]*2	
P-value (two-sided)*3		<0.0001	

*1, A stratified Cox proportional hazard model with prior lines of chemotherapy (1, 2) and geographic region (US/Canada/Europe, other regions) as stratification factors; *2, the 99% CI corresponding to the significance level was [0.49, 0.80]; *3, using a stratified log-rank test (the stratification factors are the same as those for the stratified Cox proportional hazard model), significance level (two-sided), 0.01

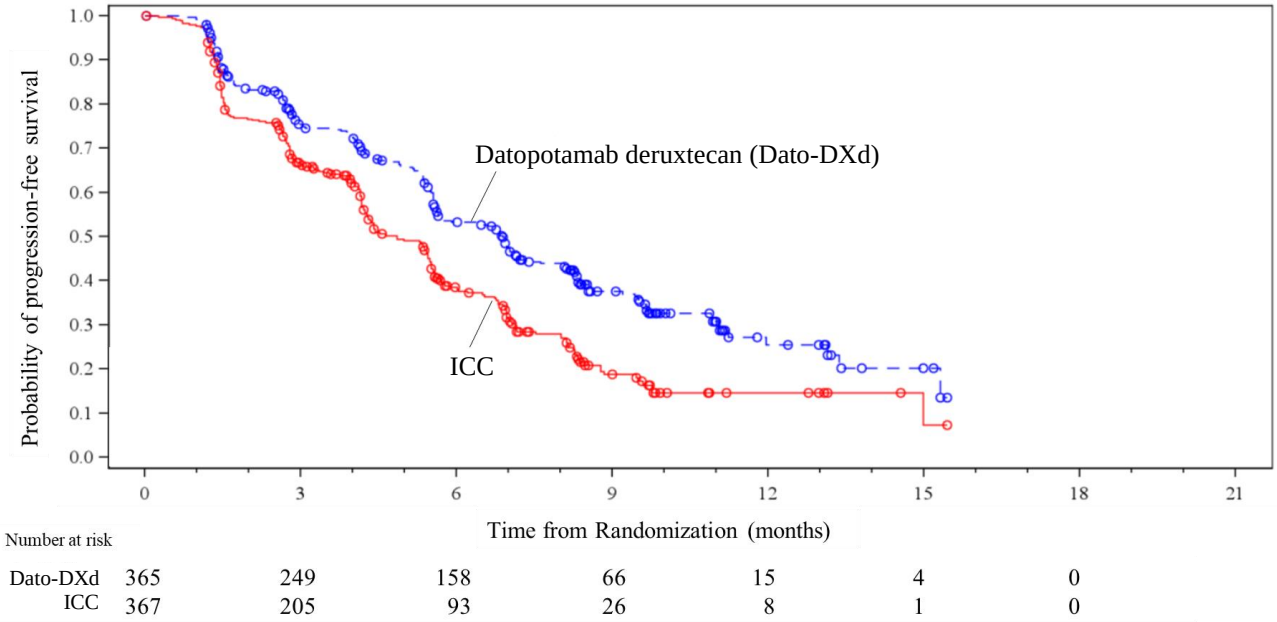

Figure 2. Kaplan-Meier plot of PFS at primary analysis (FAS, BICR assessment, data cut-off on July 17, 2023)

The results of OS, the other primary endpoint, in the first interim (data cut-off on July [redacted], 2023) and the second interim (data cut-off on [redacted], 20[redacted]) analyses are shown in Table 25 and Table 26, respectively, and their Kaplan-Meier plots are shown in Figure 3 and Figure 4, respectively. The superiority of datopotamab deruxtecan over ICC was not demonstrated.

Table 25. The first interim analysis results of OS (FAS, data cut-off on July 17, 2023)

	Datopotamab deruxtecan		ICC
Number of subjects	365		367
Number of events (%)	80 (21.9)		91 (24.8)
Median [95% CI] (months)	16.1 [16.1, —]		— [16.5, —]
Hazard ratio [95% CI]*1		0.84 [0.62, 1.14]*2	
P-value (two-sided)*3		0.2615	

"—," Unable to estimate; *1, a stratified Cox proportional hazard model with prior lines of chemotherapy (1, 2) and geographic region (US/Canada/Europe, other regions) as stratification factors; *2, the 99.94% CI corresponding to the significance level was [0.49, 1.43]; *3, using a stratified log-rank test (the stratification factors are the same as those for the stratified Cox proportional hazard model), significance level (two-sided), 0.000608

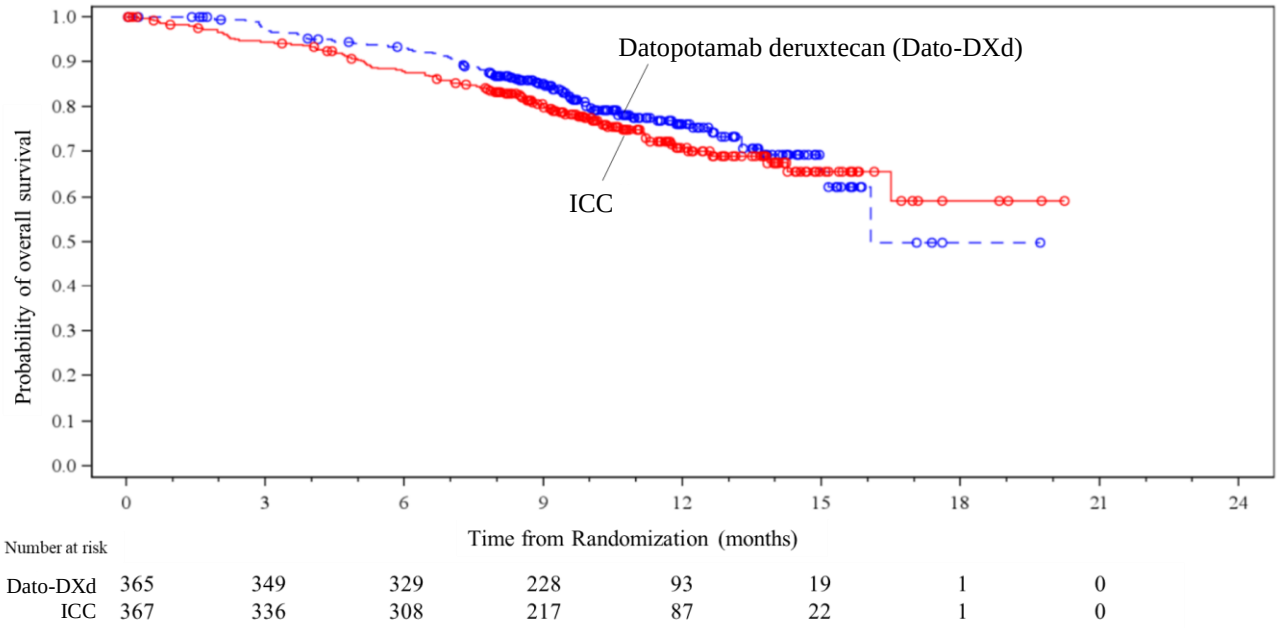

Figure 3. Kaplan-Meier plot of OS at the first interim analysis (FAS, data cut-off on July 17, 2023)

Table 26. The second interim analysis results of OS (FAS, data cut-off on [redacted])

	Datopotamab deruxtecan	ICC
Number of subjects	365	367
Number of events (%)	195 (53.4)	200 (54.5)
Median [95% CI] (months)	19.0 [17.4, 20.2]	18.2 [17.3, 19.9]
Hazard ratio [95% CI][*1]	0.93 [0.76, 1.13][*2]	
P-value (two-sided)[*3]	0.4712	

"—," Unable to estimate; *1, a stratified Cox proportional hazard model with prior lines of chemotherapy (1, 2), geographic region (US/Canada/Europe, other regions), and prior treatment with/without a CDK4/6 inhibitor as stratification factors; 2*, the 96.52% CI corresponding to the significance level was [0.75, 1,15]; *3, using a stratified log-rank test (the stratification factors are the same as those for the stratified Cox proportional hazard model), significance level (two-sided), 0.0348

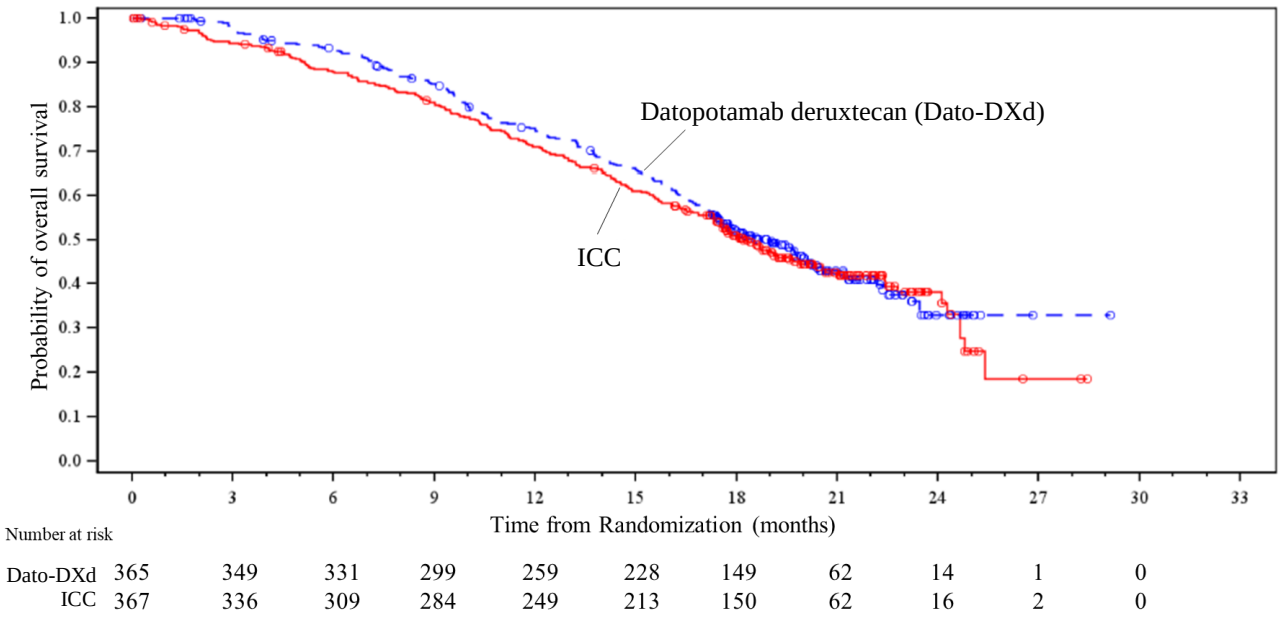

Figure 4. Kaplan-Meier plot of OS at the second interim analysis (FAS, data cut-off on [redacted])

The safety analysis revealed deaths in 5 of 365 subjects (1.4%) in the datopotamab deruxtecan group and 14 of 367 subjects (3.8%) in the ICC group (none of Japanese patients died) during treatment or within 35 days after the last dose of datopotamab deruxtecan. Other than deaths due to disease progression (5 subjects in the datopotamab deruxtecan group and 11 subjects in the ICC group), the causes of death were febrile neutropenia, respiratory distress, and sepsis (1 subject each) in the ICC group. A causal relationship to the study drug could not be ruled out for febrile neutropenia (1 subject).

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA decided to conduct efficacy and safety reviews mainly focusing on Study TB01. PMDA also decided to conduct a systematic efficacy review in Japanese patients mainly focusing on Study TB01, etc. based on the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), Amendment to "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice, Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated December 10, 2021), and "General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1, dated June 12, 2018).

7.R.2 Efficacy

Based on the following discussions, PMDA concluded that the efficacy of datopotamab deruxtecan in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy has been demonstrated.

7.R.2.1 Selection of comparator group

The applicant's explanation about the comparator group in Study TB01:

In the clinical practice guidelines published in Japan and other countries at the time of planning Study TB01,[26)] descriptions on pharmacological therapies recommended for patients with unresectable or recurrent HR-positive, HER2-negative breast cancer were as follows:

(1) If taxane- or anthracycline-based chemotherapy regimens were not used in the perioperative period, any of these agents that had not been used in the perioperative period were strongly recommended as the first-line or second-line therapy for unresectable or recurrent breast cancer.

(2) For patients who had received at least one of the prior taxane- or anthracycline-based chemotherapy regimens, agents such as eribulin, capecitabine, gemcitabine, and vinorelbine, etc. were recommended, and single agent therapy was not recommended.

Given the recommendation described in (1), patients with unresectable or recurrent breast cancer who had received 1 or 2 lines of prior chemotherapy in Study TB01 were considered to have received at least one of the prior taxane- or anthracycline-based chemotherapy regimens. Thus, and in line with (2), eribulin, capecitabine, gemcitabine, and vinorelbine were selected as control drugs in Study TB01.

26) Clinical Practice Guidelines for Breast Cancer in Japan (2018); ESMO (ABC 5) Guidelines (2020), and other guidelines

PMDA's view:

The applicant's explanation is largely acceptable. Meanwhile, the recommended patient population for datopotamab deruxtecan is discussed in Section "7.R.4 Clinical positioning and indication" based on the prior treatment of patients enrolled in Study TB01.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the primary endpoints of Study TB01:

In patients with unresectable or recurrent breast cancer, prolonged PFS will delay the time to tumor exacerbation, thus it will lead to delay in the worsening of clinical symptoms due to disease progression. This is considered clinically meaningful, and therefore, PFS was also selected as a primary endpoint of Study TB01, in addition to OS.

PMDA's view

Given that treatment for the patients in Study TB01 was aimed at life expansion, its primary endpoint should preferably have been OS alone. Nevertheless, the applicant explained their view on clinical meaningfulness of prolonged PFS in these patients, which is reasonable. At PMDA, the efficacy evaluation of datopotamab deruxtecan was conducted with attention to the OS results in Study TB01 as well.

7.R.2.3 Efficacy evaluation results

The applicant's explanation about the efficacy results in Study TB01:

The superiority of datopotamab deruxtecan over ICC was investigated for PFS per BICR assessment, one of the primary endpoints [see Section 7.1.1.2]. The results for OS, the other primary endpoint, did not demonstrate the superiority of datopotamab deruxtecan over ICC; however, there was no trend towards a decrease in OS in the datopotamab deruxtecan group compared to that in the ICC group [see Section 7.1.1.2]. There was a difference between the two groups in the percentage of patients who did not receive the study drug (1.4% [5 of 365 subjects] in the datopotamab deruxtecan group and 4.4% [16 of 367 subjects] in the ICC group).[27)] However, no clear difference was observed between the analysis results which took into account the impact of patients who did not receive the study drug[28)] and the results of the primary PFS analysis and the first interim OS analysis [see Section 7.1.1.2].

The following subsections summarize the efficacy results for (1) ICC agent-based subgroup selected before randomization; (2) TROP-2 expression status subgroup; and (3) Japanese population.

(1) ICC agent-based subgroup selected before randomization

27) The reasons for not receiving the study drug were "death" (2 subjects), "withdrawal of consent" (2 subjects), and "adverse events" (1 subject) in the datopotamab deruxtecan group; "withdrawal of consent" (11 subjects), "death" (2 subjects), "unknown" (2 subjects), "investigator's decision" (1 subject) in the ICC group.

28) In an analysis, patients censored without receiving the study drug were censored at data cut-off date. The results showed that the PFS assessed by BICR hazard ratio [95% CI] of datopotamab deruxtecan to ICC was 0.71 [0.59, 0.85] and the OS hazard ratio [95% CI] of datopotamab deruxtecan to ICC was 0.86 [0.63, 1.16].

Table 27 shows the efficacy results of the subgroups. The OS results in the group with capecitabine tended to differ from other groups. However, there were only a small number of patients with capecitabine, and many patients were censored. Furthermore, a foreign phase III study in patients with unresectable or recurrent breast cancer who had received prior chemotherapy reported no clear difference in OS between capecitabine and eribulin (*J Clin Oncol.* 2015;33:594-601). Given these outcomes, the OS results do not deny the efficacy of datopotamab deruxtecan in the group with capecitabine. In the results of analysis[29] that took into account the impact of subsequent therapy in the group with capecitabine, the OS hazard ratio [95% CI] was 1.37 [0.66, 2.89].

Table 27. The analysis results of PFS per BICR assessment and OS in the ICC subgroup based on agents selected before randomization (FAS, data cut-off on July 17, 2023)

	Agent	Treatment	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
PFS	Eribulin	Datopotamab deruxtecan	210	129 (61.4)	6.8 [5.6, 8.1]	0.62 [0.48, 0.79]
		ICC	220	143 (65.0)	4.4 [4.2, 5.5]	
	Capecitabine	Datopotamab deruxtecan	68	35 (51.5)	7.2 [5.6, 13.4]	0.83 [0.53, 1.31]
		ICC	76	42 (55.3)	7.2 [6.7, 8.3]	
	Gemcitabine	Datopotamab deruxtecan	33	18 (54.5)	5.6 [2.7, 12.0]	0.51 [0.26, 0.98]
		ICC	33	21 (63.6)	3.9 [1.7, 5.5]	
	Vinorelbine	Datopotamab deruxtecan	54	30 (55.6)	6.6 [4.9, —]	0.39 [0.23, 0.66]
		ICC	38	29 (76.3)	3.5 [1.5, 5.3]	
OS	Eribulin	Datopotamab deruxtecan	210	44 (21.0)	16.1 [15.0, —]	0.75 [0.50, 1.11]
		ICC	220	55 (25.0)	16.5 [14.3, —]	
	Capecitabine	Datopotamab deruxtecan	68	17 (25.0)	— [—, —]	1.48 [0.72, 3.12]
		ICC	76	13 (17.1)	— [—, —]	
	Gemcitabine	Datopotamab deruxtecan	33	10 (30.3)	12.6 [9.6, —]	— [—, —]
		ICC	33	9 (27.3)	— [10.4, —]	
	Vinorelbine	Datopotamab deruxtecan	54	9 (16.7)	— [—, —]	0.38 [0.16, 0.87]
		ICC	38	14 (36.8)	— [9.2, —]	

"—," Unable to estimate; *, a non-stratified Cox proportional hazard model

(2) TROP-2 expression status subgroup

Table 28 shows the efficacy results based on TROP-2 expression status assessed by an exploratory assay planned in advance in Study TB01. The assay was conducted in a patient population whose tumor tissue samples were able to provide TROP-2 expression status data (277 subjects [75.9%] in the datopotamab deruxtecan group and 268 subjects [73.0%] in the ICC group). Although OS results in the Low TROP-2 expression group reflected different trends from those in the Medium and High TROP-2 expression groups, the PFS results as well as objective response rate[30] were consistent regardless of TROP-2

[29] In the group in which capecitabine was chosen as an agent for those assigned to ICC before randomization, the proportion of patients who received subsequent therapy with ADC (T-DXd or sacituzumab govitecan [SG, genetical recombination]) was higher in the ICC group (9.2%) than in the datopotamab deruxtecan group (4.4%). Accordingly, an analysis was performed on patients who received subsequent therapy with ADC (T-DXd or SG) by censoring at the time of the subsequent therapy.

[30] The results for objective response rate in the datopotamab deruxtecan group in Study TB01 was 32.5%, 39.7%, and 37.0% in Low, Medium, and High TROP-2 groups, respectively.

expression status. Based on these, etc., datopotamab deruxtecan is expected to be effective regardless of TROP-2 expression status.

Table 28. The analysis results of PFS and OS by TROP-2 expression status (H-score[*1]) (data cut-off on July 17, 2023)

	TROP-2 expression	Treatment	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio[*2] [95% CI]	*P*-value for interaction (two-sided)[*3]
PFS	Low (H-score, 0-99)	Datopotamab deruxtecan	80	52 (65.0)	5.6 [4.9, 8.3]	0.78 [0.52, 1.17]	0.4845
		ICC	78	51 (65.4)	5.3 [4.0, 5.6]		
	Medium (H-score, 100-199)	Datopotamab deruxtecan	151	82 (54.3)	7.1 [6.6, 8.4]	0.53 [0.40, 0.72]	
		ICC	150	101 (67.3)	4.6 [4.2, 5.6]		
	High (H-score, 200-300)	Datopotamab deruxtecan	46	26 (56.5)	5.7 [4.2, —]	0.71 [0.40, 1.26]	
		ICC	40	25 (62.5)	4.4 [2.7, 7.1]		
OS	Low (H-score, 0-99)	Datopotamab deruxtecan	80	23 (28.8)	— [13.3, —]	1.15 [0.62, 2.14]	0.4107
		ICC	78	19 (24.4)	— [16.5, —]		
	Medium (H-score, 100-199)	Datopotamab deruxtecan	151	26 (17.2)	— [15.1, —]	0.62 [0.37, 1.02]	
		ICC	150	38 (25.3)	— [14.3, —]		
	High (H-score, 200-300)	Datopotamab deruxtecan	46	12 (26.1)	16.1 [13.7, —]	0.92 [0.39, 2.22]	
		ICC	40	10 (25.0)	— [11.2, —]		

"—," Unable to estimate; *1, H-score = [0 × (percentage of cells without staining) + 1 × (percentage of cells with staining intensity 1+) + 2 × (percentage of cells with staining intensity 2+) + 3 × (percentage of cells with staining intensity 3+)]; the staining intensity was classified into weak (1+), moderate (2+), and strong (3+); *2, a stratified Cox proportional hazard model with prior lines of chemotherapy (1, 2) and geographic region (US/Canada/Europe, other regions) as stratification factors for the Low and Medium groups; a stratified Cox proportional hazard model with geographic region (US/Canada/Europe, other regions) as a stratification factor for the High group; *3, a stratified Cox proportional hazard model with treatment, TROP-2 expression status, and treatment-by-TROP-2 expression status interaction as covariates, and geographic region (US/Canada/Europe, other regions) as a stratification factor.

(3) Japanese population

The primary analysis results of PFS in the Japanese population and their Kaplan-Meier plots are presented in Table 29 and Figure 5, respectively. The first interim analysis results of OS and their Kaplan-Meier plots are presented in Table 30 and Figure 6, respectively. Although the OS in the Japanese population tended to differ from those in the overall population, the analysis that took into account the impact of subsequent therapy[31)] yielded the OS hazard ratio [95% CI] of 1.13 [0.39, 3.49]. Furthermore, considering that the PFS and the objective response rate [32)] did not differ markedly between the overall and Japanese populations, datopotamab deruxtecan is also expected to be effective in Japanese patients.

31) Because in the Japanese population, the percentage of patients who received subsequent therapy with ADC (T-DXd) in the ICC group (26.3%) was higher than that in the datopotamab deruxtecan group (3.1%), an analysis was performed on patients who received subsequent therapy ADC (T-DXd) by censoring at the time of implementing the subsequent therapy.

32) The objective response rate in the datopotamab deruxtecan group in Study TB01 was 36.4% for overall population and 40.6% for Japanese population.

Table 29. The results for primary analysis of PFS in Japanese population (FAS, BICR assessment, data cut-off on July 17, 2023)

	Datopotamab deruxtecan	ICC
Number of subjects	32	38
Number of events (%)	23 (71.9)	29 (76.3)
Median [95% CI] (months)	5.6 [4.2, 7.0]	5.4 [2.8, 7.2]
Hazard ratio [95% CI]*	0.79 [0.45, 1.37]	

*, A non-stratified Cox proportional hazard model

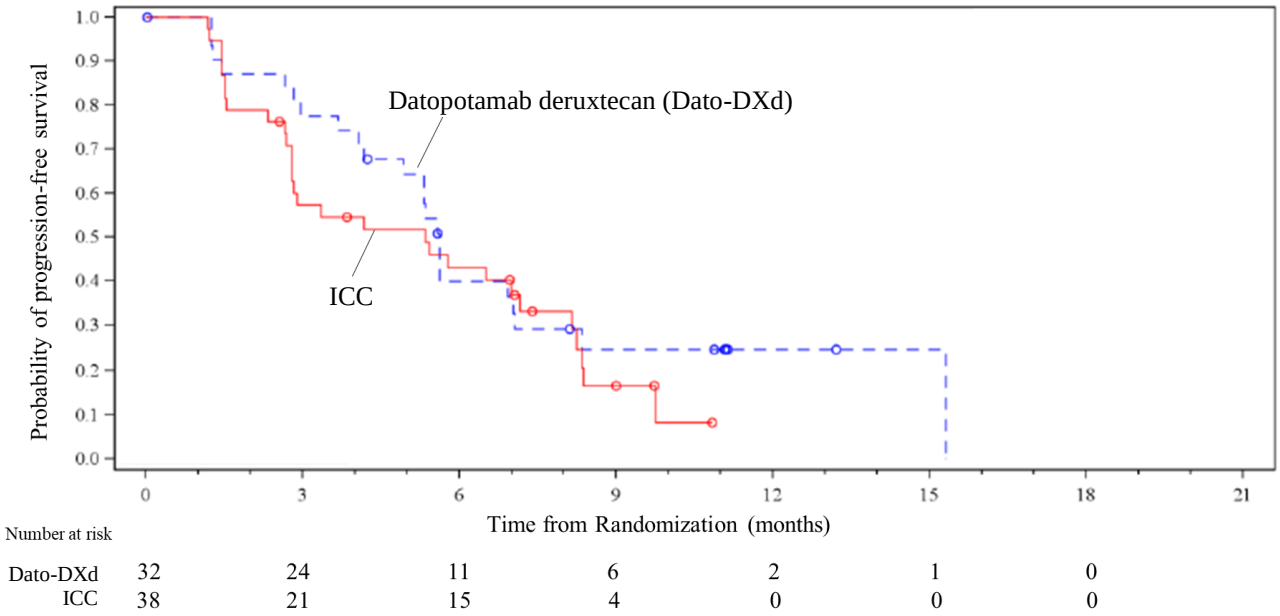

Figure 5. Kaplan-Meier plot of PFS in Japanese population at the primary analysis (FAS, BICR assessment, data cut-off on July 17, 2023)

Table 30. The results of the first interim analysis of OS in Japanese population (FAS, data cut-off on July 17, 2023)

	Datopotamab deruxtecan	ICC
Number of subjects	32	38
Number of events (%)	9 (28.1)	6 (15.8)
Median [95% CI] (months)	15.0 [11.4, —]	13.8 [13.8, —]
Hazard ratio [95% CI]*	1.49 [0.53, 4.51]	

"—," Unable to estimate; *, a non-stratified Cox proportional hazard model

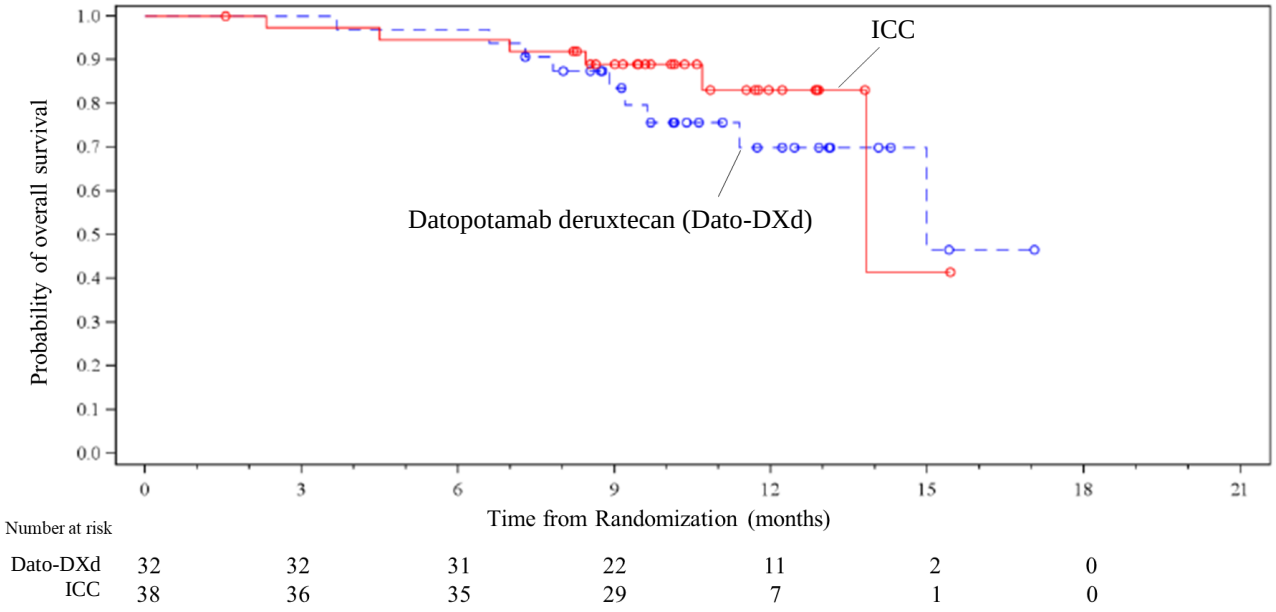

Figure 6. Kaplan-Meier plot of OS in Japanese population at the first interim analysis (FAS, data cut-off on July 17, 2023)

PMDA's view:

The efficacy of datopotamab deruxtecan has been demonstrated in the treatment of patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who received chemotherapy for the following reasons:

- In Study TB01, the results for PFS per BICR assessment, one of the primary endpoints, demonstrated the superiority of datopotamab deruxtecan over ICC, and a clinically significant level of response was observed.
- The results for OS, the other primary endpoint in Study TB01, did not show any trend towards a decrease in the datopotamab deruxtecan group compared to the ICC group.
- The small number of Japanese patients treated with datopotamab deruxtecan in Study TB01 precludes strict evaluation of the efficacy of datopotamab deruxtecan in Japanese patients based on the results of Study TB01. However, PFS assessed by BICR, one of the primary endpoints in Study TB01, did not show different trends between the overall and Japanese populations, thus datopotamab deruxtecan is also expected to be effective in Japanese patients.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events and other findings observed in clinical studies"]

On the basis of the discussions in the following sections, PMDA has concluded that corneal disorder, ILD, infusion-related reactions, and myelosuppression require particular attention during datopotamab deruxtecan treatment.

Although the use of datopotamab deruxtecan requires particular attention to these adverse events, PMDA concluded that patients should be able to tolerate datopotamab deruxtecan under appropriate monitoring, adverse event management, and dose interruption, etc. by a physician with sufficient knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profiles

The applicant's explanation about the safety profiles of datopotamab deruxtecan based on the safety data from Study TB01:

Table 31 summarizes the safety data from Study TB01. Table 32 shows adverse events that occurred at specified levels of incidences[33)] in the datopotamab deruxtecan group.

Table 31. Summary of safety data (Study TB01, data cut-off on July 17, 2023)

	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
All adverse events	350 (97.2)	337 (96.0)
Grade ≥3 adverse events	117 (32.5)	190 (54.1)
Adverse events resulting in death	0	3 (0.9)
Serious adverse events	54 (15.0)	64 (18.2)
Adverse events leading to treatment discontinuation	11 (3.1)	10 (2.8)
Adverse events leading to dose interruption	78 (21.7)	120 (34.2)
Adverse events leading to dose reduction	83 (23.1)	113 (32.2)

33) All adverse events, ≥10%; "adverse events leading to treatment discontinuation, ≥0.5%; other categories, ≥1%

Table 32. Adverse events occurring at a specified incidence or higher* in the datopotamab deruxtecan group (Study TB01, data cut-off on July 17, 2023)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
All adverse events		
Nausea	201 (55.8)	95 (27.1)
Stomatitis	184 (51.1)	50 (14.2)
Alopecia	136 (37.8)	78 (22.2)
Constipation	121 (33.6)	60 (17.1)
Fatigue	99 (27.5)	71 (20.2)
Dry eye	87 (24.2)	46 (13.1)
Vomiting	86 (23.9)	41 (11.7)
Decreased appetite	57 (15.8)	56 (16.0)
Anaemia	56 (15.6)	86 (24.5)
Asthenia	55 (15.3)	59 (16.8)
AST increased	55 (15.3)	59 (16.8)
COVID-19	55 (15.3)	47 (13.4)
Cough	48 (13.3)	32 (9.1)
Diarrhoea	38 (10.6)	66 (18.8)
Punctate keratitis	38 (10.6)	23 (6.6)
ALT increased	37 (10.3)	50 (14.2)
Grade ≥3 adverse events		
Stomatitis	23 (6.4)	9 (2.6)
Anaemia	9 (2.5)	12 (3.4)
AST increased	9 (2.5)	4 (1.1)
Fatigue	8 (2.2)	8 (2.3)
Urinary tract infection	6 (1.7)	2 (0.6)
ALT increased	5 (1.4)	1 (0.3)
Nausea	5 (1.4)	2 (0.6)
Asthenia	5 (1.4)	5 (1.4)
Decreased appetite	5 (1.4)	3 (0.9)
Hypertension	5 (1.4)	2 (0.6)
Vomiting	4 (1.1)	4 (1.1)
Blood alkaline phosphatase increased	4 (1.1)	0
Pulmonary embolism	4 (1.1)	4 (1.1)
Syncope	4 (1.1)	1 (0.3)
Serious adverse events		
Urinary tract infection	5 (1.4)	2 (0.6)
COVID-19	4 (1.1)	3 (0.9)
Adverse events leading to treatment discontinuation		
Interstitial lung disease	3 (0.8)	0
Fatigue	2 (0.6)	0
Pneumonitis	2 (0.6)	0
Adverse events leading to dose interruption		
COVID-19	12 (3.3)	14 (4.0)
Stomatitis	6 (1.7)	3 (0.9)
Fatigue	5 (1.4)	2 (0.6)
Interstitial lung disease	5 (1.4)	0
Infusion related reaction	5 (1.4)	0
Adverse events leading to dose reduction		
Stomatitis	44 (12.2)	5 (1.4)
Nausea	9 (2.5)	4 (1.1)
Weight decreased	7 (1.9)	2 (0.6)
Fatigue	6 (1.7)	6 (1.7)
Asthenia	5 (1.4)	2 (0.6)

*All adverse events category, ≥10%; adverse events leading to treatment discontinuation, ≥0.5%, other categories, ≥1%

PMDA's view:

Adverse events that occurred at a higher incidence in the datopotamab deruxtecan group in Study TB01 are likely to occur in the clinical use of datopotamab deruxtecan; therefore, patients should be monitored closely for these events while remaining aware of a potential association with datopotamab deruxtecan. However, patients should be able to tolerate datopotamab deruxtecan under appropriate monitoring, adverse event management, and dose interruption, etc. by a physician with sufficient knowledge and experience in cancer chemotherapy.

7.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of datopotamab deruxtecan between Japanese and non-Japanese populations based on the safety data from Study TB01:

Table 33 summarizes the safety data in Japanese and non-Japanese patients in the datopotamab deruxtecan group from Study TB01. Table 34 shows adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients. No adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation occurred at an incidence higher in Japanese patients than in non-Japanese patients by ≥5%.

Table 33. Summary of safety data in Japanese and non-Japanese patients (datopotamab deruxtecan group in Study TB01, data cut-off on July 17, 2023)

	Number of subjects (%)	
	Japanese patients N = 31	Non-Japanese patients N = 329
All adverse events	31 (100)	319 (97.0)
Grade ≥3 adverse events	10 (32.3)	107 (32.5)
Adverse events resulting in death	0	0
Serious adverse events	2 (6.5)	52 (15.8)
Adverse events leading to treatment discontinuation	1 (3.2)	10 (3.0)
Adverse events leading to dose interruption	6 (19.4)	72 (21.9)
Adverse events leading to dose reduction	6 (19.4)	77 (23.4)

Table 34. Adverse events* occurring at a higher incidence in Japanese patients than in non-Japanese patients (datopotamab deruxtecan group in Study TB01, data cut-off on July 17, 2023)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Japanese patients N = 31	Non-Japanese patients N = 329
All adverse events		
Nausea	21 (67.7)	180 (54.7)
Keratitis	6 (19.4)	24 (7.3)
Malaise	6 (19.4)	3 (0.9)
Dysgeusia	5 (16.1)	13 (4.0)
Grade ≥3 adverse events		
Malaise	2 (6.5)	0
Adverse events leading to dose interruption		
Interstitial lung disease	2 (6.5)	3 (0.9)
Adverse events leading to dose reduction		
Pharyngeal inflammation	2 (6.5)	0

*All adverse events, ≥10%-higher in Japanese patients; other categories, ≥5%-higher in Japanese patients

PMDA's view:

The small number of Japanese patients treated with datopotamab deruxtecan in Study TB01 precludes strict comparison of differences in safety between Japanese and non-Japanese populations. However, as some adverse events occurred more frequently in Japanese patients than in non-Japanese patients in Study TB01, the administration of datopotamab deruxtecan requires vigilance against these events. Nevertheless, patients should be able to tolerate datopotamab deruxtecan under the treatment by a physician with sufficient knowledge and experience in cancer chemotherapy.

The following sections summarize adverse events of datopotamab deruxtecan for which the need of cautionary advice should be discussed, such as events reported at a high incidence following the administration of datopotamab deruxtecan in Study TB01, etc. and those require attention in the use of T-DXd that contains DXd as with datopotamab deruxtecan.

7.R.3.3 Eye disorders

The applicant's explanation about eye disorders associated with datopotamab deruxtecan:

Table 35 and Table 36 show the incidence of eye disorders[34)] occurring in Study TB01. The median time to initial onset of eye disorders (Min, Max) in the datopotamab deruxtecan group and the ICC group was 65 days (1, 442) and 79 days (12, 253), respectively.

Table 35. Incidence of eye disorders occurring in ≥1% in either group (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)			
	Datopotamab deruxtecan N = 360		ICC N = 351	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders*	175 (48.6)	3 (0.8)	81 (23.1)	0
Dry eye	87 (24.2)	2 (0.6)	46 (13.1)	0
Punctate keratitis	38 (10.6)	1 (0.3)	23 (6.6)	0
Keratitis	30 (8.3)	0	9 (2.6)	0
Blepharitis	27 (7.5)	0	6 (1.7)	0
Lacrimation increased	26 (7.2)	0	3 (0.9)	0
Meibomian gland dysfunction	24 (6.7)	0	6 (1.7)	0
Conjunctivitis	15 (4.2)	0	3 (0.9)	0
Vision blurred	13 (3.6)	0	3 (0.9)	0
Xerophthalmia	5 (1.4)	0	1 (0.3)	0
Keratopathy	4 (1.1)	0	1 (0.3)	0

*, Total of events to be aggregated

34) Events classified as the following MedDRA PTs were captured: "acquired corneal dystrophy," "blepharitis," "conjunctivalisation," "conjunctivitis," "cornea verticillata," "corneal cyst," "corneal decompensation," "corneal defect," "corneal degeneration," "corneal deposits," "corneal disorder," "corneal endothelial cell loss," "corneal endotheliitis," "corneal epithelial microcysts," "corneal epithelial wrinkling," "corneal epithelium defect," "corneal erosion," "corneal exfoliation," "corneal infiltrates," "corneal irritation," "corneal lesion," "corneal oedema," "corneal opacity," "corneal perforation," "corneal thinning," "corneal toxicity," "dellen," "diffuse lamellar keratitis," "dry eye," "eye ulcer," "foreign body sensation in eyes," "keratitis," "keratitis interstitial," "keratitis sclerosing," "keratopathy," "keratouveitis," "lacrimation increased," "limbal stem cell deficiency," "limbal swelling," "meibomian gland dysfunction," "ocular toxicity," "photophobia," "punctate keratitis," "superior limbic keratoconjunctivitis," "tear break up time decreased," "topography corneal abnormal," "ulcerative keratitis," "vision blurred," "visual acuity reduced," "visual impairment," and "xerophthalmia."

Table 36. Incidence of serious eye disorders, etc. (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
Eye disorders leading to death	0	0
Serious eye disorders	1 (0.3)	0
Punctate keratitis	1 (0.3)	0
Eye disorders leading to treatment discontinuation	1 (0.3)	0
Dry eye	1 (0.3)	0
Eye disorders leading to dose interruption	9 (2.5)	0
Punctate keratitis	3 (0.8)	0
Visual impairment	2 (0.6)	0
Corneal lesion	1 (0.3)	0
Dry eye	1 (0.3)	0
Keratitis	1 (0.3)	0
Photophobia	1 (0.3)	0
Vision blurred	1 (0.3)	0
Ulcerative keratitis	1 (0.3)	0
Eye disorders leading to dose reduction	4 (1.1)	1 (0.3)
Dry eye	1 (0.3)	1 (0.3)
Corneal erosion	1 (0.3)	0
Keratitis	1 (0.3)	0
Punctate keratitis	1 (0.3)	0

Table 37 shows the details of patients who developed serious eye disorders[35)] for which a causal relationship to datopotamab deruxtecan could not be ruled out [36)] in the clinical studies of datopotamab deruxtecan monotherapy including Study TB01.[37)]

Table 37. List of patients who developed serious eye disorders for which a causal relationship to datopotamab deruxtecan could not be ruled out

Study ID	Age	Sex	MedDRA PT	Grade	Onset day (days)	Duration (days)	Datopotamab deruxtecan	Outcome
TB01	6[redacted]	Female	Punctate keratitis	3	63	265	Reduced	Not resolved
TP01	7[redacted]	Female	Ulcerative keratitis	3	434	121	Discontinued	Resolved
TL01	6[redacted]	Female	Vision blurred	3	439	44	Reduced	Resolved
	5[redacted]	Female	Visual acuity reduced	3	316	56	Discontinued	Resolving
			Ulcerative keratitis	3	330	64	Interrupted	Resolved

The Study TB01 protocol ver.[redacted] (dated on [redacted], 20[redacted]) required ophthalmological examination (e.g., visual acuity tests, slit lamp microscopy test, tonometry, and fundoscopy) at the time of enrollment, the end of study drug treatment, and whenever clinically indicated. However, given that ocular toxicities such as corneal disorders had been reported in multiple subjects in the clinical studies of datopotamab deruxtecan other than Study TB01, ophthalmological examination (tests including fluorescein test, in addition to the type of tests mentioned above) was required every 3 cycles in the protocol ver.[redacted] (dated on [redacted], 20[redacted]). It also strongly advised to consider avoiding the use of contact lenses and using artificial tears daily.

35) Medical Dictionary for Regulatory Activities (MedDRA) versions used to capture adverse events were ver.26.0 (Study TB01), ver.25.0 (Breast cancer cohort of Study TP01), ver.23.0 (NSCLC cohort of Study TP01), ver.26.0 (Study TL01), and ver.26.0 (Study TL05).

36) Adverse events for which the possibility that the events were caused by datopotamab deruxtecan can be reasonably explained as determined by the investigator

37) Study TB01, Study TP01, Study TL01 (a global phase III study in patients with unresectable advanced/recurrent NSCLC who have received prior chemotherapy), and Study TL05 (a global phase II study in patients with unresectable advanced/recurrent NSCLC who have received prior chemotherapy)

Corneal disorders have been reported associated with ADCs. In an ADC consisting of an anti-folate receptor α (FRα) antibody and a maytansine derivative, it has been suggested that corneal disorder may be caused by inhibition of epithelial turnover in the corneal limbal epithelium where there are nutrient vessels (*Gynecol Oncol Rep.* 2023;47:101155). Given that only a small number of corneal disorder events have been reported with T-DXd, which also contains DXd as with datopotamab deruxtecan, a relationship between corneal disorders and anti-TROP-2 antibody, the antibody component of datopotamab deruxtecan, is a possibility, however, the underlying mechanism remains unclear.

PMDA's view:
Corneal disorders occurred at a certain level of incidence in the datopotamab deruxtecan group in Study TB01, and serious corneal disorders for which a causal relationship to datopotamab deruxtecan could not be ruled out were reported from multiple subjects in the clinical studies of datopotamab deruxtecan, vigilance is required against corneal disorders during the treatment. Healthcare professionals should be appropriately reminded of the occurrence of corneal disorders in the clinical studies and advised how to deal with the events via the package insert, etc.

7.R.3.4 ILD

The applicant's explanation about ILD associated with datopotamab deruxtecan:
Of the ILD reported in Study TB01, [38)] the incidence of events reviewed and adjudicated as datopotamab deruxtecan-associated ILD events by the independent ILD adjudication committee[39)] are shown in Table 38 and Table 39. The median time to initial onset of ILD (Min, Max) in the datopotamab deruxtecan group in Study TB01 was 60 days (34, 166).

38) Events classified as the following MedDRA PTs were captured: "acute interstitial pneumonitis," "acute respiratory distress syndrome," "acute respiratory failure," "allergic eosinophilia," "alveolar lung disease," "alveolar proteinosis," "alveolitis," "alveolitis necrotising," "autoimmune lung disease," "bronchiolitis," "bronchiolitis obliterans syndrome," "chronic graft versus host disease in lung," "combined pulmonary fibrosis and emphysema," "confirmed e-cigarette or vaping product use associated lung injury," "diffuse alveolar damage," "eosinophilia myalgia syndrome," "eosinophilic granulomatosis with polyangiitis," "eosinophilic pneumonia," "eosinophilic pneumonia acute," "eosinophilic pneumonia chronic," "granulomatous pneumonitis," "hypersensitivity pneumonitis," "idiopathic interstitial pneumonia," "idiopathic pneumonia syndrome," "idiopathic pulmonary fibrosis," "immune-mediated lung disease," "interstitial lung abnormality," "interstitial lung disease," "low lung compliance," "lung infiltration," "lung opacity," "necrotising bronchiolitis," "obliterative bronchiolitis," "organising pneumonia," "pleuroparenchymal fibroelastosis," "pneumonitis," "probable e-cigarette or vaping product use associated lung injury," "progressive massive fibrosis," "pulmonary fibrosis," "pulmonary necrosis," "pulmonary radiation injury," "pulmonary sarcoidosis," "pulmonary toxicity," "pulmonary vasculitis," "radiation alveolitis," "radiation bronchitis," "radiation fibrosis - lung," "radiation pneumonitis," "respiratory failure," "restrictive pulmonary disease," "rheumatoid arthritis-associated interstitial lung disease," "rheumatoid lung," "sarcoidosis," "small airways disease," and "transfusion-related acute lung injury."

39) The independent ILD adjudication committee reviewed adverse events that occurred in clinical studies and were captured as ILD of applicable MedDRA PTs. When a case was determined to be ILD, the onset day, severity, and causal relationship with the study drug were assessed by the independent ILD adjudication committee.

Table 38. Incidence of ILD (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)			
	Datopotamab deruxtecan N = 360		ICC N = 351	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD*	12 (3.3)	3 (0.8)	0	0
Pneumonitis	7 (1.9)	3 (0.8)	0	0
Interstitial lung disease	5 (1.4)	0	0	0

*, Total of events to be aggregated

Table 39. Incidence of serious ILD, etc. (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
ILD leading to death	0	0
Serious ILD	4 (1.1)	0
Pneumonitis	3 (0.8)	0
Interstitial lung disease	1 (0.3)	0
ILD leading to treatment discontinuation	5 (1.4)	0
Interstitial lung disease	3 (0.8)	0
Pneumonitis	2 (0.6)	0
ILD leading to dose interruption	3 (0.8)	0
Interstitial lung disease	2 (0.6)	0
Pneumonitis	1 (0.3)	0
ILD leading to dose reduction	1 (0.3)	0
Pneumonitis	1 (0.3)	0

Table 40 provides the details of patients who developed serious ILD[35] for which a causal relationship to datopotamab deruxtecan could not be ruled out[36] in the clinical studies[37] of datopotamab deruxtecan monotherapy including Study TB01.

Table 40. List of patients who developed serious ILD for which a causal relationship to datopotamab deruxtecan could not be ruled out

Study ID	Age	Sex	Population	Primary disease	MedDRA PT	Grade[*1]	Onset[*1] (days)	Duration[*1] (days)	Datopotamab deruxtecan	Outcome[*2]
TB01	6[redacted]	F	Non-Japanese	Breast cancer	Interstitial lung disease	2	84	1	Discontinued	Not resolved
	5[redacted]	F	Non-Japanese	Breast cancer	Pneumonitis	5	37	55	Discontinued	Not resolved[*3]
	6[redacted]	F	Non-Japanese	Breast cancer	Pneumonitis	3	37	31	Not applicable	Not resolved
	6[redacted]	F	Non-Japanese	Breast cancer	Pneumonitis	3	34	191	Discontinued	Not resolved
TP01	7[redacted]	F	Japanese	NSCLC	Pneumonitis	2	21	72	Discontinued	Not resolved
	7[redacted]	M	Japanese	NSCLC	Pneumonitis	2	41	29	Interrupted	Resolved
	5[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	4	128	7	Unchanged	Death
	4[redacted]	F	Non-Japanese	Breast cancer	Pneumonitis	3	254	28	Discontinued	Not resolved
TL01	6[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	5	24	25	Discontinued	Not resolved
					Respiratory failure	5	28	22	Unchanged	Resolving
					Pneumonitis	5	49	1	Not applicable	Death
	7[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	5	34	27	Discontinued	Death
	7[redacted]	F	Non-Japanese	NSCLC	Pneumonitis	4	24	13	Discontinued	Resolving
					Pneumonitis	4	37	174	Not applicable	Not resolved
	6[redacted]	F	Non-Japanese	NSCLC	Respiratory failure	2	122	7	Interrupted	Resolved
	5[redacted]	F	Non-Japanese	NSCLC	Pneumonitis	3	379	84	Interrupted	Resolved
	4[redacted]	F	Non-Japanese	NSCLC	Interstitial lung disease	5	36	7	Discontinued	Resolved[*3]
	8[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	1	266	6	Discontinued	Resolved
	8[redacted]	M	Japanese	NSCLC	Pneumonitis	5	32	3	Not applicable	Not resolved[*3]
					Pneumonitis	5	35	57	Not applicable	Not resolved[*3]
	7[redacted]	M	Japanese	NSCLC	Pneumonitis	3	55	2	Unchanged	Not resolved
					Pneumonitis	3	57	32	Interrupted	Resolving
					Pneumonitis	3	89	43	Not applicable	Resolving
	6[redacted]	M	Japanese	NSCLC	Pneumonitis	2	323	430	Discontinued	Resolving
	8[redacted]	F	Japanese	NSCLC	Pneumonitis	5	101	27	Discontinued	Not resolved[*3]
	5[redacted]	M	Japanese	NSCLC	Pneumonitis	2	67	63	Discontinued	Resolved
	6[redacted]	M	Japanese	NSCLC	Pneumonitis	5	43	9	Discontinued	Not resolved
					Pneumonitis	5	52	1	Not applicable	Death
	7[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	2	72	23	Interrupted	Resolved
	4[redacted]	M	Non-Japanese	NSCLC	Interstitial lung disease	2	12	17	Discontinued	Resolving
					Interstitial lung disease	2	29	32	Not applicable	Resolving
	6[redacted]	M	Non-Japanese	NSCLC	Pneumonitis	5	238	23	Discontinued	Not resolved[*3]
TL05	3[redacted]	M	Non-Japanese	NSCLC	Dyspnoea	5	7	4	Interrupted	Resolved
					Dyspnoea	5	20	8	Discontinued	Resolved[*3]

*1, Assessed by the independent ILD adjudication committee; *2, assessed by the investigator; *3, It was initially reported as death of non-ILD cause. Later, the independent ILD adjudication committee determined the event as death due to ILD (Grade 5).

PMDA's view:

In Study TB01, ILD occurred in the datopotamab deruxtecan group but did not occur in the ICC group. In the clinical studies of datopotamab deruxtecan, ILD leading to death and serious ILD for which a causal

relationship to datopotamab deruxtecan could be reasonably explained occurred in multiple patients; caution has been advised for ILD associated with agents such as T-DXd, which contains DXd as with datopotamab deruxtecan, and irinotecan hydrochloride hydrate, which, like DXd, is a camptothecin derivative. Given these factors, vigilance is required against ILD during the treatment. Therefore, healthcare professionals should be appropriately reminded of the occurrence of ILD in the clinical studies and advised how to deal with these events via the package insert, etc.

7.R.3.5 Infusion-related reactions

The applicant's explanation about infusion-related reactions associated with datopotamab deruxtecan:

Table 41 and Table 42 show the incidence of infusion-related reactions in Study TB01.[40] The median time to initial onset of infusion-related reactions (Min, Max) in Study TB01 was 10.5 days (1, 234) in the datopotamab deruxtecan group and 32 days (1, 176) in the ICC group.

Table 41. Incidence of infusion reaction (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)			
	Datopotamab deruxtecan N = 360		ICC N = 351	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction*	32 (8.9)	1 (0.3)	12 (3.4)	0
Pruritus	10 (2.8)	0	0	0
Infusion related reaction	10 (2.8)	0	0	0
Pyrexia	6 (1.7)	0	8 (2.3)	0
Rash	4 (1.1)	0	3 (0.9)	0
Bronchospasm	1 (0.3)	1 (0.3)	0	0
Urticaria	1 (0.3)	0	0	0
Hypotension	0	0	1 (0.3)	0

* Total of events to be aggregated

Table 42. Incidence of serious infusion reaction, etc. (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
Infusion reaction resulting in death	0	0
Serious infusion reaction	0	0
Infusion reaction leading to treatment discontinuation	1 (0.3)	0
Bronchospasm	1 (0.3)	0
Infusion reaction leading to dose interruption	5 (1.4)	0
Infusion related reaction	5 (1.4)	0
Infusion reaction leading to dose reduction	0	0

Table 43 shows the details of patients who developed serious infusion-related reactions[35] for which a causal relationship to datopotamab deruxtecan could not be ruled out[36] in the clinical studies[37] of datopotamab deruxtecan monotherapy including Study TB01.

[40] Included events of the following MedDRA PTs that occurred on the day of study drug administration: "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "angioedema," "bronchospasm," "circulatory collapse," "flushing," "hypersensitivity," "hypotension," "infusion related hypersensitivity reaction," "infusion related reaction," "polymers allergy," "pruritus," "pyrexia," "rash," "rash maculo-papular," "shock," "type I hypersensitivity," "urticaria," and "wheezing."

Table 43. List of patients who developed a serious infusion reaction for which a causal relationship to datopotamab deruxtecan could not be ruled out

Study ID	Age	Sex	MedDRA PT	Grade	Onset day (days)	Duration (days)	Datopotamab deruxtecan	Outcome
TP01	6[redacted]	F	Infusion related reaction	3	1	3	Discontinued	Resolved
TL05	5[redacted]	F	Hypersensitivity	2	63	2	Unchanged	Resolved

In the clinical studies[37)] of datopotamab deruxtecan monotherapy including Study TB01, prophylactic antihistamine and acetaminophen were required to reduce infusion-related reactions associated with datopotamab deruxtecan treatment, and the protocol specified prophylactic treatment with adrenal corticosteroid was initiated as necessary.[41)] In 45.0% (162 of 360) of patients in the datopotamab deruxtecan group in Study TB01 received prophylactic adrenal corticosteroid.

PMDA's view:

While prophylactic treatment was administered to reduce infusion-related reactions caused by datopotamab deruxtecan, infusion-related reactions occurred at a certain incidence in the datopotamab deruxtecan group in Study TB01; in the clinical studies of datopotamab deruxtecan, serious infusion-related reactions for which a causal relationship to datopotamab deruxtecan could not be ruled out occurred in multiple patients; datopotamab deruxtecan comprises an antibody as a component; and cases of infusion-related reactions have been reported associated with other TROP-2 targeting ADCs. Given these factors, vigilance is required against infusion-related reactions during the treatment. Therefore, healthcare professionals should be appropriately reminded of the occurrence of infusion-related reactions in the clinical studies and advised how to deal with these events via the package insert, etc.

7.R.3.6 Myelosuppression

The applicant's explanation about myelosuppression associated with datopotamab deruxtecan:

Table 44 and Table 45 show the incidence of myelosuppression in Study TB01.[42)] The median time to initial onset of myelosuppression (Min, Max) in Study TB01 was 42 days (1, 470) in the datopotamab deruxtecan group and 21 days (1, 323) in the ICC group.

41) In Study TP01, this was first specified in the protocol ver. [redacted] (dated on [redacted], 20[redacted]).

42) Included events of the following MedDRA PTs: "haemoglobin decreased," "red blood cell count decreased," "anaemia," "haematocrit decreased," "neutrophil count decreased," "neutropenia," "platelet count decreased," "thrombocytopenia," "white blood cell count decreased," "leukopenia," "lymphocyte count decreased," "lymphopenia," "pancytopenia," and "febrile neutropenia."

Table 44. Incidence of myelosuppression (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)			
	Datopotamab deruxtecan N = 360		ICC N = 351	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression*	90 (25.0)	16 (4.4)	199 (56.7)	131 (37.3)
Anaemia	56 (15.6)	9 (2.5)	86 (24.5)	12 (3.4)
Neutrophil count decreased	23 (6.4)	3 (0.8)	77 (21.9)	54 (15.4)
Neutropenia	18 (5.0)	1 (0.3)	88 (25.1)	62 (17.7)
White blood cell count decreased	17 (4.7)	2 (0.6)	41 (11.7)	16 (4.6)
Leukopenia	13 (3.6)	0	28 (8.0)	12 (3.4)
Lymphocyte count decreased	7 (1.9)	2 (0.6)	6 (1.7)	2 (0.6)
Platelet count decreased	7 (1.9)	0	20 (5.7)	6 (1.7)
Lymphopenia	7 (1.9)	0	10 (2.8)	2 (0.6)
Thrombocytopenia	3 (0.8)	0	15 (4.3)	1 (0.3)
Haemoglobin decreased	2 (0.6)	0	1 (0.3)	0
Pancytopenia	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Febrile neutropenia	0	0	8 (2.3)	8 (2.3)
Red blood cell count decreased	0	0	4 (1.1)	0

*, Total of events to be aggregated

Table 45. Incidence of serious myelosuppression, etc. (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
Myelosuppression leading to death	0	1 (0.3)
Febrile neutropenia	0	1 (0.3)
Serious myelosuppression	3 (0.8)	10 (2.8)
Anaemia	2 (0.6)	0
Pancytopenia	1 (0.3)	0
Febrile neutropenia	0	5 (1.4)
Neutropenia	0	1 (0.3)
Neutrophil count decreased	0	2 (0.6)
Platelet count decreased	0	2 (0.6)
Thrombocytopenia	0	1 (0.3)
Myelosuppression leading to treatment discontinuation	0	2 (0.6)
Neutropenia	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Myelosuppression leading to dose interruption	4 (1.1)	68 (19.4)
Anaemia	3 (0.8)	4 (1.1)
Lymphocyte count decreased	1 (0.3)	0
Febrile neutropenia	0	1 (0.3)
Leukopenia	0	6 (1.7)
Neutropenia	0	38 (10.8)
Neutrophil count decreased	0	27 (7.7)
Platelet count decreased	0	2 (0.6)
Thrombocytopenia	0	4 (1.1)
White blood cell count decreased	0	4 (1.1)
Myelosuppression leading to dose reduction	2 (0.6)	56 (16.0)
Anaemia	1 (0.3)	4 (1.1)
Neutropenia	1 (0.3)	23 (6.6)
Pancytopenia	1 (0.3)	0
Febrile neutropenia	0	3 (0.9)
Leukopenia	0	2 (0.6)
Neutrophil count decreased	0	23 (6.6)
Platelet count decreased	0	1 (0.3)
Thrombocytopenia	0	2 (0.6)
White blood cell count decreased	0	5 (1.4)

Table 46 provides the details of patients who developed serious myelosuppression[35)] for which a causal relationship to datopotamab deruxtecan could not be ruled out[36)] in the clinical studies[37)] of datopotamab deruxtecan monotherapy including Study TB01.

Table 46. List of patients who developed serious myelosuppression for which a causal relationship to datopotamab deruxtecan could not be ruled out

Study ID	Age	Sex	MedDRA PT	Grade	Onset (days)	Duration (days)	Datopotamab deruxtecan	Outcome
TB01	4[redacted]	F	Pancytopenia	3	9	18	Reduced	Resolved
	7[redacted]	F	Anaemia	3	43	19	Interrupted	Resolved
TL01	4[redacted]	M	Anaemia	3	21	4	Reduced	Resolved
	6[redacted]	M	Anaemia	3	115	93	Unchanged	Resolved
	6[redacted]	M	Neutropenia	3	8	5	Unchanged	Resolved
			Pancytopenia	3	8	13	Unchanged	Not resolved
			Febrile neutropenia	3	9	12	Unchanged	Not resolved
	7[redacted]	M	Anaemia	3	13	9	Unchanged	Resolved

PMDA's view:

Myelosuppression occurred at a certain rate in the datopotamab deruxtecan group in Study TB01. In the clinical studies of datopotamab deruxtecan, serious myelosuppression for which a causal relationship to datopotamab deruxtecan could not be ruled out occurred in multiple patients. Caution has been advised for myelosuppression associated with T-DXd, which contains DXd as with datopotamab deruxtecan. Given these factors, vigilance is required against myelosuppression during the treatment. Therefore, healthcare professionals should be appropriately reminded of the occurrence of myelosuppression in the clinical studies and advised how to deal with these events via the package insert, etc.

7.R.3.7 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with datopotamab deruxtecan:

To evaluate gastrointestinal disorders, MedDRA system organ class (SOC) "gastrointestinal disorders" and PT "decreased appetite" were captured.

Table 47 and Table 48 show the incidence of gastrointestinal disorders in Study TB01. The median time to initial onset of gastrointestinal disorders (Min, Max) in Study TB01 was 4 days (1, 210) in the datopotamab deruxtecan group and 8 days (1, 253) in the ICC group.

Table 47. Incidence of gastrointestinal disorders occurring in ≥1% in either group (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)			
	Datopotamab deruxtecan N = 360		ICC N = 351	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders*	306 (85.0)	43 (11.9)	216 (61.5)	26 (7.4)
Nausea	201 (55.8)	5 (1.4)	95 (27.1)	2 (0.6)
Stomatitis	184 (51.1)	23 (6.4)	50 (14.2)	9 (2.6)
Constipation	121 (33.6)	1 (0.3)	60 (17.1)	0
Vomiting	86 (23.9)	4 (1.1)	41 (11.7)	4 (1.1)
Decreased appetite	57 (15.8)	5 (1.4)	56 (16.0)	3 (0.9)
Diarrhoea	38 (10.6)	2 (0.6)	66 (18.8)	5 (1.4)
Abdominal pain	23 (6.4)	1 (0.3)	29 (8.3)	4 (1.1)
Dry mouth	19 (5.3)	1 (0.3)	6 (1.7)	0
Abdominal pain upper	15 (4.2)	1 (0.3)	17 (4.8)	1 (0.3)
Mouth ulceration	15 (4.2)	1 (0.3)	7 (2.0)	0
Abdominal distension	10 (2.8)	1 (0.3)	10 (2.8)	1 (0.3)
Dyspepsia	10 (2.8)	0	9 (2.6)	0
Gastritis	9 (2.5)	0	4 (1.1)	0
Haemorrhoids	9 (2.5)	0	2 (0.6)	0
Gastrooesophageal reflux disease	7 (1.9)	0	9 (2.6)	0
Odynophagia	7 (1.9)	0	1 (0.3)	0
Ascites	6 (1.7)	1 (0.3)	3 (0.9)	1 (0.3)
Dysphagia	6 (1.7)	0	0	0
Rectal haemorrhage	6 (1.7)	0	0	0
Oral pain	5 (1.4)	0	2 (0.6)	0
Toothache	5 (1.4)	0	6 (1.7)	0
Abdominal discomfort	4 (1.1)	0	3 (0.9)	0
Aphthous ulcer	4 (1.1)	0	0	0

*, Total of events to be aggregated

Table 48. Incidence of serious gastrointestinal disorders, etc. (Study TB01)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Datopotamab deruxtecan N = 360	ICC N = 351
Gastrointestinal disorders leading to death	0	0
Serious gastrointestinal disorders	5 (1.4)	8 (2.3)
Diarrhoea	2 (0.6)	1 (0.3)
Vomiting	2 (0.6)	1 (0.3)
Stomatitis	1 (0.3)	1 (0.3)
Abdominal pain	0	1 (0.3)
Ileus	0	1 (0.3)
Intestinal obstruction	0	1 (0.3)
Nausea	0	1 (0.3)
Decreased appetite	0	1 (0.3)
Neutropenic colitis	0	1 (0.3)
Gastrointestinal disorders leading to treatment discontinuation	1 (0.3)	1 (0.3)
Stomatitis	1 (0.3)	0
Anal inflammation	1 (0.3)	0
Neutropenic colitis	0	1 (0.3)
Gastrointestinal disorders leading to dose interruption	16 (4.4)	11 (3.1)
Stomatitis	6 (1.7)	3 (0.9)
Nausea	3 (0.8)	2 (0.6)
Decreased appetite	3 (0.8)	1 (0.3)
Diarrhoea	2 (0.6)	4 (1.1)
Abdominal distension	1 (0.3)	0
Abdominal pain	1 (0.3)	0
Tongue ulceration	1 (0.3)	0
Vomiting	1 (0.3)	2 (0.6)
Oral dysaesthesia	1 (0.3)	0
Intestinal obstruction	0	1 (0.3)
Faecal vomiting	0	1 (0.3)
Gastrointestinal disorders leading to dose reduction	53 (14.7)	17 (4.8)
Stomatitis	44 (12.2)	5 (1.4)
Nausea	9 (2.5)	4 (1.1)
Vomiting	3 (0.8)	1 (0.3)
Decreased appetite	3 (0.8)	1 (0.3)
Mouth ulceration	2 (0.6)	0
Constipation	1 (0.3)	2 (0.6)
Diarrhoea	1 (0.3)	8 (2.3)
Gastritis	1 (0.3)	0
Glossitis	1 (0.3)	0
Oesophagitis	1 (0.3)	0
Proctitis	1 (0.3)	0
Anal inflammation	1 (0.3)	0
Abdominal pain	0	1 (0.3)

Table 49 shows the details of patients who developed serious gastrointestinal disorders[35)] for which a causal relationship to datopotamab deruxtecan could not be ruled out[36)] in the clinical studies[37)] of datopotamab deruxtecan monotherapy including Study TB01.

Table 49. List of patients who developed serious gastrointestinal disorders for which a causal relationship to datopotamab deruxtecan could not be ruled out

Study ID	Age	Sex	MedDRA PT	Grade	Onset day (days)	Duration (days)	Datopotamab d eruxtecan	Outcome
TB01	4[redacted]	F	Vomiting	3	66	21	Not applicable	Not resolved
	6[redacted]	F	Stomatitis	3	63	419	Reduced	Resolving
TP01	5[redacted]	F	Vomiting	3	220	4	Unchanged	Resolved
			Nausea	3	221	3	Unchanged	Resolved
	3[redacted]	F	Upper gastrointestinal haemorrhage	3	3	3	Unchanged	Resolved
TL01	5[redacted]	M	Vomiting	3	23	2	Unchanged	Resolved
	6[redacted]	M	Stomatitis	4	15	26	Discontinued	Resolved
	5[redacted]	M	Oesophagitis	3	47	2	Unchanged	Resolved
	7[redacted]	M	Rectal haemorrhage	3	155	7	Unchanged	Resolved
	6[redacted]	F	Stomatitis	3	9	13	Interrupted	Resolved
	6[redacted]	F	Stomatitis	3	14	18	Reduced	Resolving
	5[redacted]	F	Vomiting	2	6	6	Unchanged	Resolved
	6[redacted]	M	Vomiting	2	11	4	Unchanged	Resolved
	6[redacted]	M	Upper gastrointestinal haemorrhage	3	5	1	Unchanged	Resolved
	6[redacted]	F	Stomatitis	3	11	7	Reduced	Resolving
	7[redacted]	F	Stomatitis	3	23	7	Unchanged	Resolving
TL05	4[redacted]	F	Stomatitis	3	15	134	Unchanged	Not resolved
	4[redacted]	F	Vomiting	2	5	2	Unchanged	Resolved
			Vomiting	2	47	2	Reduced	Resolved

In Study TB01, prophylactic use of agents such as 5-HT_3 receptor agonists, NK_1 receptor agonists, and adrenal corticosteroids was strongly recommended to reduce nausea/vomiting caused by datopotamab deruxtecan treatment. Oral care was recommended to reduce the severity of stomatitis caused by datopotamab deruxtecan treatment. The amended protocol ver.[redacted] (dated on [redacted], 20[redacted]), strongly advised to consider the use of adrenal corticosteroid-containing mouthwash.

PMDA's view:

In Study TB01, gastrointestinal disorders occurred in the datopotamab deruxtecan group at a certain rate, and in the clinical studies of datopotamab deruxtecan, serious gastrointestinal disorders for which a causal relationship to datopotamab deruxtecan could not be ruled out occurred. However, of the patients who experienced serious gastrointestinal disorders, except for stomatitis in 1 subject in Study TL01 (resolved after discontinuation of datopotamab deruxtecan treatment) and stomatitis in 1 subject in Study TL05 (not resolved while on datopotamab deruxtecan treatment), the other cases were reported as resolved or resolving while still on datopotamab deruxtecan treatment (including dose reduction/interruption). As for other events reported in multiple patients, given that (1) vomiting and stomatitis are unlikely to result in severe outcomes; and that (2) upper gastrointestinal hemorrhage resolved in a short time period while on datopotamab deruxtecan treatment, PMDA concluded that no particular cautionary statements are necessary at this point, provided that the applicant provides information for healthcare professionals by including data on the incidence of gastrointestinal disorders in the clinical studies in the package insert and other materials.

7.R.4 Clinical positioning and indication

The proposed indication of datopotamab deruxtecan and the precautions concerning indication were specified as in the table below.

Indication	Precautions concerning indication
Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy	• Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the "Clinical studies" section, and the efficacy and safety of datopotamab deruxtecan. • The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

Based on the discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following sections, PMDA concluded that the indication of datopotamab deruxtecan and the precautions concerning indication should be specified as in the table below.

Indication	Precautions concerning indication
Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy	• Datopotamab deruxtecan should be administered to patients who received prior anthracycline- or taxane-based chemotherapy. • Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the "Clinical studies" section, and the efficacy and safety of datopotamab deruxtecan. • The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

7.R.4.1 Clinical positioning of datopotamab deruxtecan and patient population

In the clinical practice guidelines and representative textbooks on clinical oncology published in Japan and other countries,[43)] there are no descriptions of datopotamab deruxtecan use in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy.

The applicant's explanation about clinical positioning and patient population of datopotamab deruxtecan:
The results of Study TB01, which was conducted in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who had received prior chemotherapy, demonstrated that datopotamab deruxtecan is clinically useful [see Sections 7.R.2 and 7.R.3]. Therefore, it is considered that datopotamab deruxtecan can be positioned as a treatment option for such patients.

Study TB01 targeted patients with unresectable or recurrent breast cancer treated with 1 or 2 lines of prior chemotherapy. In view of this, prior treatment of patients enrolled in the clinical studies will be detailed in the "Clinical studies" section of the package insert, with cautionary advice in the "Precautions Concerning Indication" section that the patient's eligibility should be determined with a thorough understanding of the given details. Currently, no efficacy or safety data of datopotamab deruxtecan are available from clinical studies for use in neoadjuvant or adjuvant therapy for breast cancer. Thus, the use of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy is not recommended, which will be also mentioned.

43) ESMO Clinical Practice Guidelines (2021), NCCN Guidelines in Oncology, Breast Cancer (v.3.2024), NCI-PDQ (ver. October 11, 2024), Clinical Practice Guidelines for Breast Cancer in Japan (2022), DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (12th ed., J.B. Lippencott Company, 2018, USA), New Clinical Oncology [in Japanese] (seventh revised edition, Nankodo), and other publications

Accordingly, the package insert provides the details of prior treatment of patients enrolled in Study TB01 in the "Clinical studies" section, and the proposed indication and precautions concerning indication specified as in the table below.

Indication	Precautions concerning indication
Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy	• Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the "Clinical studies" section, and the efficacy and safety of datopotamab deruxtecan. • The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

No clinical study data have been obtained to compare the efficacy and safety of datopotamab deruxtecan with the treatment options shown below. Because of this and other factors, the choice between datopotamab deruxtecan and the other options remains unclear and specific treatment will be selected according to the patient's condition taking the efficacy and safety of each agent into account.

- T-DXd for patients with unresectable or recurrent HER2-low breast cancer who have received prior chemotherapy
- Olaparib and talazoparib for patients with unresectable or recurrent germline *BRCA*-mutation positive, HER2-negative breast cancer who have received prior chemotherapy

In the Clinical Practice Guidelines for Breast Cancer in Japan (2022 edition), if taxane- or anthracycline-based chemotherapy regimens were not used in the perioperative period, either one of these agents that was not used in the perioperative period is strongly recommended as first-line or second-line therapy for unresectable or recurrent breast cancer. Given this situation, PMDA asked the applicant to explain the clinical positioning of datopotamab deruxtecan in patients who have received neither taxane- nor anthracycline-based regimens as prior chemotherapy.

The applicant's explanation:

In Study TB01, 87.8% (643 of 732) of enrolled patients had received at least one of the prior taxane- or anthracycline-based chemotherapy regimens. Table 50 shows the efficacy results by prior taxane/anthracycline-based chemotherapy status (regardless of perioperative or non-perioperative period, or unresectable or recurrent breast cancer). Datopotamab deruxtecan is expected to be effective in patients who have received neither taxane- nor anthracycline-based prior chemotherapy. Therefore, datopotamab deruxtecan can also be recommended for such patients.

Table 50. Results of PFS and OS analyses per BICR in subgroup for with/without taxane/anthracycline-based prior chemotherapy (regardless of perioperative or non-perioperative period, or unresectable or recurrent breast cancer) (FAS, data cut-off on July 17, 2023)

	Prior treatment status	Treatment	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]*
PFS	Both taxane and anthracycline	Datopotamab deruxtecan	204	117 (57.4)	5.7 [5.5, 8.1]	0.69 [0.54, 0.89]
		ICC	211	129 (61.1)	4.4 [4.2, 5.5]	
	Taxane and/or anthracycline	Datopotamab deruxtecan	319	190 (59.6)	6.7 [5.6, 7.1]	0.66 [0.54, 0.81]
		ICC	324	208 (64.2)	4.5 [4.2, 5.5]	
	Neither taxane nor anthracycline	Datopotamab deruxtecan	46	22 (47.8)	10.9 [7.0, —]	0.45 [0.24, 0.81]
		ICC	43	27 (62.8)	5.5 [4.0, 8.3]	
OS	Both taxane and anthracycline	Datopotamab deruxtecan	204	49 (24.0)	— [16.1, —]	0.81 [0.55, 1.18]
		ICC	211	59 (28.0)	16.5 [16.5, —]	
	Taxane and/or anthracycline	Datopotamab deruxtecan	319	75 (23.5)	16.1 [15.1, —]	0.87 [0.64, 1.19]
		ICC	324	84 (25.9)	— [16.5, —]	
	Neither taxane nor anthracycline	Datopotamab deruxtecan	46	5 (10.9)	— [—, —]	Not calculated
		ICC	43	7 (16.3)	— [—, —]	

"—," Unable to estimate; *, a non-stratified Cox proportional hazard model

PMDA's view:

The applicant's explanation is largely acceptable. However, datopotamab deruxtecan is recommended for patients who have received at least one of the taxane- and anthracycline-based prior chemotherapy regimens, and it is difficult to recommend datopotamab deruxtecan for patients with no taxane- or anthracycline-based prior chemotherapy, based on several factors including the following:

- In the Clinical Practice Guidelines for Breast Cancer in Japan (2022 edition), if taxane- or anthracycline-based chemotherapy regimens were not used in the perioperative period, one of these agents that was not used in the perioperative period is strongly recommended as first-line or second-line therapy for unresectable or recurrent breast cancer, and these agents are more strongly recommended compared to the agents established for the ICC group in Study TB01.
- No results have been obtained from (1) clinical studies that compared the efficacy and safety of datopotamab deruxtecan with those of taxane-based chemotherapy in patients who had not received taxane-based chemotherapy in the perioperative period, or (2) clinical studies that compared the efficacy and safety of datopotamab deruxtecan with those of anthracycline-based chemotherapy in patients who had not received anthracycline-based chemotherapy. Thus, it is not recommended to give priority to datopotamab deruxtecan over taxane-based or anthracycline-based chemotherapy for patients who have not received taxane-based chemotherapy or in patients who have not received anthracycline-based chemotherapy.
- The majority of patients enrolled in Study TB01 had received at least one of the prior taxane-based and anthracycline-based prior chemotherapy regimens.

On the basis of the above, PMDA has concluded that the indication of datopotamab deruxtecan should be defined as "patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer

who have received prior chemotherapy" as per the proposed one, and the following statements will be presented in the "Precautions Concerning Indication" section:

- Datopotamab deruxtecan should be administered to patients who have received prior anthracycline- or taxane-based chemotherapy.
- Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the "Clinical studies" section, and the efficacy and safety of datopotamab deruxtecan.
- The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

7.R.5 Dosage and administration

The proposed dosage and administration of datopotamab deruxtecan and the precautions concerning dosage and administration section were specified as in the table below.

Dosage and administration	Precautions concerning dosage and administration
The usual adult dosage is 6.0 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes.	• The efficacy and safety of datopotamab deruxtecan have not been established in its combination use with other antineoplastic agents. • To reduce infusion-related reactions, prophylactic antihistamine and acetaminophen should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary. • To alleviate nausea associated with datopotamab deruxtecan, the use of antiemetics (e.g., dexamethasone and 5-HT_3 receptor agonist or NK_1 receptor agonist) should be considered before or after the administration of datopotamab deruxtecan as necessary. • Criteria for dose interruption, reduction, and treatment discontinuation after adverse drug reaction [see Section 7.R.5.2]

Based on the discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following sections, PMDA has concluded that the dosage and administration of datopotamab deruxtecan and the precautions concerning dosage and administration should be specified as in the table below.

Dosage and administration	Precautions concerning dosage and administration
The usual adult dosage is 6 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes. The dose may be reduced according to the patient's condition.	• The efficacy and safety of datopotamab deruxtecan have not been established in its combination use with other antineoplastic agents. • To reduce infusion-related reactions, prophylactic antihistamine and antipyretic-analgesic should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary. • Criteria for dose interruption, reduction, and treatment discontinuation after adverse drug reaction [see Section 7.R.5.2]

7.R.5.1 The dosage regimen of datopotamab deruxtecan

The applicant's explanation about the dosage regimen of datopotamab deruxtecan:

Study TB01 was conducted using a dosage regimen that was established taking into account several factors including those shown below. The results of Study TB01, which was conducted in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who had received prior chemotherapy, demonstrated that datopotamab deruxtecan is clinically useful [see Sections 7.R.2 and 7.R.3]. Therefore, the proposed dosage regimen for datopotamab deruxtecan was determined based on the dosage regimen in Study TB01.

- In the dose escalation part of the NSCLC cohort in Study TP01, the MTD of datopotamab deruxtecan was determined to be 8 mg/kg Q3W. However, based on the following results obtained later in the dose escalation part and dose expansion part in Study TP01, the RP2D of datopotamab deruxtecan was determined to be 6 mg/kg Q3W.
  - In the NSCLC cohort in Study TP01, the incidence of Grade ≥3 adverse events, ILD, and other adverse events for which a causal relationship to datopotamab deruxtecan could not be ruled out was lower in the 4 mg/kg and 6 mg/kg groups than in the 8 mg/kg group.[44)]
  - In the NSCLC cohort in Study TP01, the objective response rate tended to be higher in the 6 mg/kg group than in the 4 mg/kg group.[45)]

No data have been obtained from clinical studies that evaluated the efficacy and safety of datopotamab deruxtecan used in combination with other antineoplastic agents. Therefore, the use of datopotamab deruxtecan with other antineoplastic agents is not recommendable, and such advice will be offered. In addition, based on Study TB01, prophylactic treatment against infusion-related reactions and nausea caused by datopotamab deruxtecan will also be advised.

Based on the above, the proposed dosage and administration of datopotamab deruxtecan and the precautions concerning dosage and administration were specified as in the table below.

Dosage and administration	Precautions concerning dosage and administration
The usual adult dosage is 6.0 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes.	• The efficacy and safety of datopotamab deruxtecan have not been established in its combination use with other antineoplastic agents. • To reduce infusion reactions, prophylactic antihistamine and acetaminophen should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary. • To alleviate nausea associated with datopotamab deruxtecan, the use of antiemetics (e.g., dexamethasone and 5-HT_3 receptor agonist or NK_1 receptor agonist) should be considered before or after the administration of datopotamab deruxtecan as necessary. • Criteria for dose interruption, reduction, and treatment discontinuation after adverse drug reaction [see Section 7.R.5.2]

PMDA's view:

PMDA largely accepted the applicant's explanation. However, in Study TB01, the dose was to be reduced depending on the patient's condition including the occurrence of adverse events [see Section 7.R.5.2]. Thus, the dosage and administration should also mention this. There is little need to mention the prophylactic measures against nausea associated with datopotamab deruxtecan as a precaution concerning dosage and administration, assuming that datopotamab deruxtecan will be used by physicians with sufficient knowledge and experience in cancer chemotherapy.

44) The incidence of Grade ≥3 adverse events was 30.0% in the 4 mg/kg group, 54.0% in the 6 mg/kg group, and 58.8% in the 8 mg/kg group; and the incidence of ILD for which a causal relationship to datopotamab deruxtecan could not be ruled out was 10.0% in the 4 mg/kg group, 6.0% in the 6 mg/kg group, and 13.8% in the 8 mg/kg group.

45) The objective response rate assessed by BICR was 22.0% in the 4 mg/kg group, 26.0% in the 6 mg/kg group, and 23.8% in the 8 mg/kg group.

Taken together, the dosage and administration and the precautions concerning dosage and administration section should be specified as in the table below.

Dosage and administration	Precautions concerning dosage and administration
The usual adult dosage is 6 mg/kg (body weight) od datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes. The dose may be reduced according to the patient's condition.	• The efficacy and safety of datopotamab deruxtecan have not been established in its combination with other antineoplastic agents. • To reduce infusion reactions, prophylactic antihistamine and antipyretic-analgesic should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary. • Criteria for dose interruption, reduction, and treatment discontinuation after adverse drug reaction [see Section 7.R.5.2]

7.R.5.2 Criteria for dose interruption, reduction, treatment discontinuation

The applicant's explanation about the criteria for dose interruption, reduction, and treatment discontinuation of datopotamab deruxtecan:

In Study TB01, the criteria for dose interruption, reduction, and treatment discontinuation of datopotamab deruxtecan in case of adverse events were specified, and datopotamab deruxtecan was demonstrated to be clinically useful when the criteria were adhered to. Therefore, descriptions concerning general treatment and examinations were removed from the Study TB01 criteria, while dose interruption and reduction, and treatment discontinuation criteria were proposed with the following additional changes as precautions concerning dosage and administration.

- In Study TB01, Grade 2 stomatitis required thorough prophylactic measures and symptomatic treatment [see Section 7.R.3.7], and dose interruption or reduction should be considered when clinically necessary. In the proposed criteria, to be more cautious, this has been modified to: dose interruption until stomatitis resolves to Grade ≤1, and the treatment may be resumed at the same dose for the first onset or at a reduced dose for recurrence. In Study TB01, Grade 3 stomatitis required dose interruption until resolution to Grade ≤1, and treatment could be resumed (1) at the same dose after prophylactic measures and symptomatic treatment if such measures had not been sufficiently given, or (2) at a reduced dose if prophylactic measures and symptomatic treatment had already been sufficiently given. However, in the proposed criteria, datopotamab deruxtecan is to be resumed at a reduced dose regardless of whether prophylactic measures and symptomatic treatment are provided.
- In Study TB01, Grade 1 infusion-related reaction required the reduction of infusion rate to 50% of the infusion rate at event onset. If no new symptoms of infusion-related reaction were observed after reduction, the next infusion could be administered at the same infusion rate at event onset. Also, Grade 2 infusion-related reaction required the interruption of infusion, which could be resumed after resolution to Grade ≤1 at 50% of the infusion rate at event onset; and the next infusion was to be administered at 50% of the infusion rate at event onset and if no new symptoms of infusion-related reaction were observed, the subsequent infusions could be administered at the same infusion rate as that at event onset. In the proposed criteria, however, the infusion rate after Grade 1 or 2 infusion-related reactions is to be determined according to the patient's condition instead of providing specific criteria.
- In Study TB01, Grade 3 infusion-related reaction required the discontinuation of datopotamab deruxtecan. However, in the clinical studies of datopotamab deruxtecan including Study

TB01,[46] datopotamab deruxtecan was re-administered to 3 of 6 subjects who had developed Grade 3 infusion-related reactions, and 2 of them experienced recurred reactions, which were non-serious and Grade <3. This suggests that datopotamab deruxtecan can be re-administered. Thus, infusion rate reduction or dose interruption will be advised.

- Study TB01 specified the criteria for dose interruption, reduction, treatment discontinuation for Grade 3 or 4 neutrophil count decreased, white blood cell count decreased, febrile neutropenia, anemia, platelet count decreased, nausea/vomiting, and diarrhea, and Grade 4 lymphocyte count decreased. However, the majority of these events were non-serious[47] and datopotamab deruxtecan treatment was able to continue[48] in Study TB01. Therefore, these events can be managed in routine clinical practice, and these criteria will not be specified.
- In Study TB01, apart from the major adverse events,[49] (1) other Grade 3 adverse events required dose interruption until resolution to Grade ≤1 as necessary and (2) treatment discontinuation was advised for Grade 4 adverse events. These are general routine clinical practice and will not be specified.

PMDA's view:

The applicant's explanation is largely acceptable. However, for infusion-related reactions and myelosuppression, adverse events of datopotamab deruxtecan that require particular attention [see Section 7.R.3], criteria should be set based on those in Study TB01. For adverse drug reactions without separate criteria for dose interruption, reduction, and treatment discontinuation, the criteria should also be specified based on Study TB01.

Accordingly, the criteria for dose interruption, reduction, and treatment discontinuation described above should be modified as shown below and presented in the precautions concerning dosage and administration:

- If an adverse reaction to datopotamab deruxtecan occurs, the doses must be interrupted, reduced, or the treatment must be discontinued based on the following criteria.

Dose level for reductions

First dose reduction	4 mg/kg
Second dose reduction	3 mg/kg
Third dose reduction	Discontinue treatment

[46] Study TB01, Study TP01, Study TL01 (global phase III study in patients with unresectable advanced or recurrent NSCLC who have received prior chemotherapy), Study TL02 (global phase Ib study in patients with unresectable advanced or recurrent NSCLC who have received prior chemotherapy), and Study TL05 (global phase II study in patients unresectable advanced or recurrent NSCLC who have received prior chemotherapy)

[47] Of the following adverse events occurring in Study TB01: neutrophil count decreased/white blood cell count decreased, febrile neutropenia, anaemia, platelet count decreased, nausea/vomiting, diarrhoea, and lymphocyte count decreased, those classified as serious adverse events were anaemia, vomiting, and diarrhoea (2 subjects each).

[48] Of the following adverse events occurring in Study TB01: neutrophil count decreased/white blood cell count decreased, febrile neutropenia, anaemia, platelet count decreased, nausea/vomiting, diarrhoea, and lymphocyte count decreased, adverse events that led to dose interruption were anaemia (3 subjects), nausea (3 subjects), diarrhoea (2 subjects), vomiting (1 subject), and lymphocyte count decreased (1 subject); adverse events that led to dose reduction were nausea (9 subjects), vomiting (3 subjects), neutrophil count decreased (1 subject), anaemia (1 subject), and diarrhoea (1 subject). None of the reported adverse events led to treatment discontinuation.

[49] ILD, ocular surface toxicities, stomatitis, infusion related reaction, neutrophil count decreased/white blood cell count decreased, anaemia, platelet count decreased, febrile neutropenia, lymphocyte count decreased, nausea/vomiting, and diarrhoea

Criteria for dose interruption, reduction, or treatment discontinuation after adverse drug reaction

Adverse reaction	Severity[Note)]	Action
ILD	Grade 1	Interrupt the dose until complete resolution. Treatment may be resumed at the same dose level after ≤28 day interruption, or at 1 lower dose level after >28 day interruption.
	Grade 2, 3, or 4	Discontinue treatment.
Keratitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level. For recurrence, interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.
Infusion-related reaction	Grade 1	Reduce infusion rate by 50%. If no new infusion-related reaction develops, the next infusion may be administered at the rate at event onset.
	Grade 2	Interrupt infusion. After resolution to Grade ≤1, infusion may be resumed at the rate reduced by 50%. Administer the next infusion at the rate reduced by 50% from that at event onset. If no new infusion-related reaction develops, the subsequent infusions may be administered at the rate at event onset.
	Grade 3 or 4	Discontinue treatment.
Neutrophil count decreased, white blood cell count decreased, anaemia	Grade 3	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same or 1 lower dose level.
Platelet count decreased	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
Other adverse drug reactions	Grade 3	Interrupt the dose until resolution to Grade ≤1 or baseline. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.

Note) According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver.5.0.

7.R.6 Risk management plan (draft)

The risk management plan (RMP) for datopotamab deruxtecan will be developed in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012) and "Risk Management Plan templates, instructions and publication" (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1 dated March 18, 2022).

In view of the discussions in Sections "5.5 Reproductive and developmental toxicity" and "7.R.3 Safety" and the adverse drug reactions[50)] to irinotecan hydrochloride hydrate, a camptothecin derivative as with DXd contained in datopotamab deruxtecan, for which cautions have been advised, PMDA concluded that the RMP (draft) for datopotamab deruxtecan should include the safety specifications presented in Table 51.

50) Bone marrow function suppression, severe diarrhea/enterocolitis, intestinal perforation/gastrointestinal hemorrhage/intestinal obstruction, interstitial pneumonia, shock/anaphylaxis, hepatic dysfunction/jaundice, acute kidney injury, thromboembolism, cerebral infarction, myocardial infarction/anginal attack, and ventricular extrasystoles

Table 51. Safety and efficacy specifications in the RMP (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Corneal disorder • ILD • Infusion-related reactions • Myelosuppression	• Embryo-fetal toxicity • Severe diarrhea/enterocolitis • Intestinal perforation, gastrointestinal hemorrhage, intestinal obstruction • Anaphylaxis • Hepatic dysfunction • Renal dysfunction • Thromboembolism • Cardiac disorders	None
Efficacy specification		
None		

7.R.7 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plan:

The applicant has planned to conduct post-marketing surveillance covering all patients who will be receiving datopotamab deruxtecan to keep track of the occurrence of associated adverse events, etc. in post-marketing clinical use.

Based on the occurrence of adverse events in Study TB01, the safety specification for the survey includes corneal disorder and ILD, which are considered to require particular attention during datopotamab deruxtecan treatment.

A planned sample size of 300 patients and a follow-up period of 18 months have been selected taking into account the occurrence in Study TB01 of each adverse event to be included in the safety specification for the survey.

PMDA's view:

No TROP-2-directed DXd ADCs have been approved in Japan. Nevertheless, given the factors below, post-marketing surveillance needs not be conducted immediately after approval in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy, where the provision of information to medical settings about adverse events of datopotamab deruxtecan of particular attention (corneal disorder, ILD, infusion-related reactions, and myelosuppression), collection of datopotamab deruxtecan safety information, and implementation of appropriate safety measures based on current and future information are ensured through early post-marketing phase vigilance and routine pharmacovigilance activities.

- Based on the clinical study data, the safety profiles of datopotamab deruxtecan is clear to some extent.
- Currently, none of the adverse events of datopotamab deruxtecan requiring particular attention are subject to active information collection through post-marketing surveillance.
- Based on the results from non-clinical and clinical studies of datopotamab deruxtecan, currently there are no specific issues of adverse events pertaining to binding to TROP-2 that need to be clarified through post-marketing surveillance.

- Because T-DXd [51)] also contains DXd as with datopotamab deruxtecan, a certain amount of post-marketing data on DXd are available,[52)] which have raised no new DXd-related safety concerns among Japanese patients.

However, if any new issue to address arises after the market launch of datopotamab deruxtecan, the implementation of post-marketing surveillance, etc. should be discussed promptly as additional pharmacovigilance activities.

7.2 Adverse events and other findings observed in clinical studies

The following sections discuss the major adverse events other than death reported in the clinical study results submitted for safety evaluation, which are discussed in Section "7.1 Evaluation data." Where there are no applicable events, their descriptions are omitted.

7.2.1 Global phase I study (Study TP01)

7.2.1.1 Dose escalation part

7.2.1.1.1 NSCLC cohort

Adverse events occurred in 3 of 4 subjects (75.0%) in the 0.27 mg/kg group, 5 of 5 subjects (100%) in the 0.5 mg/kg group, 6 of 7 subjects (85.7%) in the 1 mg/kg group, 6 of 6 subjects (100%) in the 2 mg/kg group, 29 of 29 subjects (100%) in the 4 mg/kg group, 33 of 34 subjects (97.1%) in the 6 mg/kg group, 36 of 36 subjects (100%) in the 8 mg/kg group, and 8 of 8 subjects (100%) in the 10 mg/kg group. Among these, a causal relationship to the study drug could not be ruled out in 1 of 4 subjects (25.0%) in the 0.27 mg/kg group, 3 of 5 subjects (60.0%) in the 0.5 mg/kg group, 4 of 7 subjects (57.1%) in the 1 mg/kg group, 4 of 6 subjects (66.7%) in the 2 mg/kg group, 27 of 29 subjects (93.1%) in the 4 mg/kg group, 28 of 34 subjects (82.4%) in the 6 mg/kg group, 35 of 36 subjects (97.2%) in the 8 mg/kg group, and 8 of 8 subjects (100%) in the 10 mg/kg group. Adverse events occurring in ≥30% of subjects in any group are presented in Table 52 and Table 53.

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51) Of the adverse events requiring particular attention when datopotamab deruxtecan is administered, ILD, infusion-related reactions, and myelosuppression are listed as adverse events requiring particular attention for T-DXd (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated July 6, 2023).

52) Trastuzumab deruxtecan was approved with the following indications: unresectable or recurrent HER2-positive breast cancer in patients who have previously been treated with chemotherapy (March 25, 2020 and November 24, 2022); unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy (September 25, 2020); unresectable or recurrent HER2-low breast cancer in patients who have previously been treated with chemotherapy (March 27, 2023); and unresectable advanced or recurrent *HER2 (ERBB2*) mutation-positive non-small cell lung cancer that has progressed after cancer chemotherapy (August 23, 2023). The applicant submitted a report on the post-marketing surveillance results in patients with unresectable or recurrent breast cancer (1,767 patients included in safety analyses) and in patients with unresectable advanced or recurrent gastric cancer (1,126 patients included in safety analyses).

Table 52. Adverse events occurring in ≥30% of subjects in any group

SOC PT (MedDRA ver.23.0)	Number of subjects (%)							
	0.27 mg/kg N = 4		0.5 mg/kg N = 5		1 mg/kg N = 7		2 mg/kg N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (75.0)	2 (50.0)	5 (100)	4 (80.0)	6 (85.7)	2 (28.6)	6 (100)	3 (50.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Cancer pain	0	0	2 (40.0)	1 (20.0)	0	0	0	0
Blood and lymphatic system disorders								
Anaemia	0	0	2 (40.0)	0	2 (28.6)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	1 (25.0)	0	1 (20.0)	0	2 (28.6)	0	3 (50.0)	0
Respiratory, thoracic and mediastinal disorders								
Cough	0	0	0	0	2 (28.6)	0	2 (33.3)	0
Dyspnoea	0	0	3 (60.0)	1 (20.0)	0	0	1 (16.7)	0
Gastrointestinal disorders								
Nausea	1 (25.0)	0	0	0	0	0	4 (66.7)	0
Constipation	0	0	2 (40.0)	0	2 (28.6)	0	1 (16.7)	0
Vomiting	0	0	0	0	0	0	3 (50.0)	0
General disorders and administration site conditions								
Fatigue	0	0	4 (80.0)	1 (20.0)	4 (57.1)	0	2 (33.3)	1 (16.7)
Malaise	0	0	2 (40.0)	0	0	0	0	0
Pain	0	0	2 (40.0)	0	0	0	2 (33.3)	1 (16.7)
Investigations								
Weight decreased	0	0	2 (40.0)	0	0	0	1 (16.7)	0
Injury, poisoning and procedural complications								
Infusion related reaction	0	0	1 (20.0)	0	0	0	2 (33.3)	0

Table 53. Adverse events occurring in ≥30% of subjects in any group

SOC PT (MedDRA ver.23.0)	Number of subjects (%)							
	4 mg/kg N = 29		6 mg/kg N = 34		8 mg/kg N = 36		10 mg/kg N = 8	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	29 (100)	11 (37.9)	33 (97.1)	17 (50.0)	36 (100)	23 (63.9)	8 (100)	4 (50.0)
Metabolism and nutrition disorders								
Decreased appetite	5 (17.2)	0	10 (29.4)	1 (2.9)	12 (33.3)	0	4 (50.0)	0
Eye disorders								
Dry eye	6 (20.7)	0	6 (17.6)	0	11 (30.6)	0	3 (37.5)	0
Gastrointestinal disorders								
Nausea	15 (51.7)	0	22 (64.7)	2 (5.9)	22 (61.1)	1 (2.8)	6 (75.0)	0
Stomatitis	12 (41.4)	0	18 (52.9)	1 (2.9)	18 (50.0)	1 (2.8)	4 (50.0)	1 (12.5)
Constipation	7 (24.1)	0	11 (32.4)	0	10 (27.8)	0	1 (12.5)	0
Vomiting	4 (13.8)	0	9 (26.5)	1 (2.9)	14 (38.9)	0	4 (50.0)	0
Skin and subcutaneous tissue disorders								
Alopecia	11 (37.9)	0	17 (50.0)	0	16 (44.4)	0	4 (50.0)	0
Rash	6 (20.7)	0	4 (11.8)	0	11 (30.6)	0	3 (37.5)	0
Skin hyperpigmentation	1 (3.4)	0	2 (5.9)	0	2 (5.6)	0	3 (37.5)	0
General disorders and administration site conditions								
Fatigue	7 (24.1)	0	13 (38.2)	0	17 (47.2)	1 (2.8)	5 (62.5)	0
Mucosal inflammation	3 (10.3)	1 (3.4)	6 (17.6)	1 (2.9)	5 (13.9)	3 (8.3)	4 (50.0)	1 (12.5)
Investigations								
ALT increased	1 (3.4)	0	2 (5.9)	1 (2.9)	4 (11.1)	0	3 (37.5)	0
White blood cell count decreased	0	0	3 (8.8)	0	1 (2.8)	0	3 (37.5)	0

Serious adverse events occurred in 2 of 4 subjects (50.0%) in the 0.27 mg/kg group, 2 of 5 subjects (40.0%) in the 0.5 mg/kg group, 1 of 6 subjects (16.7%) in the 2 mg/kg group, 8 of 29 subjects (27.6%) in the 4 mg/kg group, 16 of 34 subjects (47.1%) in the 6 mg/kg group, 18 of 36 subjects (50.0%) in the 8 mg/kg group, and 2 of 4 subjects (50.0%) in the 10 mg/kg group. Serious adverse events occurring in ≥3 subjects in any group were pneumonia (3 subjects, 8.8%) in the 6 mg/kg group, and a causal relationship to the study drug was ruled out.

Adverse events leading to treatment discontinuation of the study drug occurred in 4 of 29 subjects (13.8%) in the 4 mg/kg group, 4 of 34 subjects (11.8%) in the 6 mg/kg group, 9 of 36 subjects (25.0%) in the 8 mg/kg group, and 1 of 8 subjects (12.5%) in the 10 mg/kg group. Adverse events leading to treatment discontinuation of the study drug that occurred in ≥2 subjects in any group were pneumonitis (3 subjects, 8.3%) in the 8 mg/kg group, and a causal relationship to the study drug could not be ruled out.

7.2.1.1.2 Breast cancer cohort

Adverse events occurred in all subjects. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 41 of 42 subjects (97.6%) in the 6 mg/kg group and 2 of 2 subjects (100%) in the 8 mg/kg group. Table 54 shows the adverse events occurring in ≥20% of subjects in the 6 mg/kg group.

Table 54. Adverse events occurring in ≥20% of subjects in the 6 mg/kg group

SOC PT (MedDRA ver.25.0)	Number of subjects (%)			
	6 mg/kg N = 42		8 mg/kg* N = 2	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	42 (100)	21 (50.0)	2 (100)	2 (100)
Nervous system disorders				
Headache	11 (26.2)	0	0	0
Gastrointestinal disorders				
Stomatitis	31 (73.8)	5 (11.9)	1 (50.0)	0
Nausea	28 (66.7)	1 (2.4)	1 (50.0)	0
Vomiting	17 (40.5)	2 (4.8)	0	0
Constipation	9 (21.4)	0	1 (50.0)	0
Skin and subcutaneous tissue disorders				
Alopecia	14 (33.3)	0	2 (100)	0
General disorders and administration site conditions				
Fatigue	15 (35.7)	3 (7.1)	0	0

*, Adverse events of any grade occurring only in the 8 mg/kg group at an incidence of ≥20% were cellulitis, urinary tract infection, diverticulitis, iron deficiency anaemia, hypokalaemia, hyperglycaemia, anxiety, insomnia, dizziness, myoclonus, dry eye, retinal exudates, corneal toxicity, deep vein thrombosis, embolism, dysphagia, dyspepsia, hepatic steatosis, pruritus, skin burning sensation, back pain, musculoskeletal chest pain, dysuria, vulvovaginal discomfort, vulvovaginal pruritus, pyrexia, oedema peripheral, lymphocyte count decreased, neutrophil count decreased, weight decreased, infusion related reaction, procedural pain, skin wound, and wound complication (1 subject each, 50.0%). Among these events, Grade ≥3 adverse events were urinary tract infection, iron deficiency anaemia, and musculoskeletal chest pain (1 subject each, 50.0%).

Serious adverse events occurred in 7 of 42 subjects (16.7%) in the 6 mg/kg group and 2 of 2 subjects (100%) in the 8 mg/kg group. There were no serious adverse events occurring in ≥2 subjects.

An adverse event led to treatment discontinuation of the study drug in 1 of 44 subjects (2.4%). This event occurred in 1 subject (pneumonitis) in the 6 mg/kg group. A causal relationship to the study drug could not be ruled out for the event.

7.2.1.2 Dose expansion part

7.2.1.2.1 NSCLC cohort

Adverse events occurred in 20 of 21 subjects (95.2%) in the 4 mg/kg group, 16 of 16 subjects (100%) in the 6 mg/kg group, and 44 of 44 subjects (100%) in the 8 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 20 of 21 subjects (95.2%) in the 4 mg/kg group, 13 of 16 subjects (81.3%) in the 6 mg/kg group, and 43 of 44 subjects (97.7%) in the 8 mg/kg group. Table 55 shows adverse events occurring in ≥20% of subjects in any group.

Table 55. Adverse events occurring in ≥20% of subjects in any group

SOC PT (MedDRA ver.23.0)	Number of subjects (%)					
	4 mg/kg N = 21		6 mg/kg N = 16		8 mg/kg N = 44	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	20 (95.2)	4 (19.0)	16 (100)	10 (62.5)	44 (100)	24 (54.5)
Blood and lymphatic system disorders						
Anaemia	2 (9.5)	2 (9.5)	4 (25.0)	0	13 (29.5)	4 (9.1)
Metabolism and nutrition disorders						
Decreased appetite	5 (23.8)	0	3 (18.8)	0	9 (20.5)	0
Eye disorders						
Dry eye	2 (9.5)	0	2 (12.5)	0	12 (27.3)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	3 (14.3)	0	1 (6.3)	0	10 (22.7)	3 (6.8)
Cough	2 (9.5)	0	0	0	10 (22.7)	1 (2.3)
Gastrointestinal disorders						
Stomatitis	9 (42.9)	0	12 (75.0)	0	26 (59.1)	3 (6.8)
Nausea	9 (42.9)	0	10 (62.5)	0	21 (47.7)	0
Vomiting	3 (14.3)	0	0	0	15 (34.1)	0
Constipation	1 (4.8)	0	1 (6.3)	0	13 (29.5)	1 (2.3)
Skin and subcutaneous tissue disorders						
Rash	4 (19.0)	0	0	0	10 (22.7)	0
Alopecia	2 (9.5)	0	4 (25.0)	0	22 (50.0)	0
General disorders and administration site conditions						
Mucosal inflammation	3 (14.3)	0	0	0	11 (24.0)	1 (2.3)
Fatigue	1 (4.8)	0	1 (6.3)	0	21 (47.7)	1 (2.3)
Investigations						
Weight decreased	0	0	0	0	9 (20.5)	0
Injury, poisoning and procedural complications						
Infusion related reaction	5 (23.8)	0	2 (12.5)	1 (6.3)	14 (31.8)	0

Serious adverse events occurred in 2 of 21 subjects (9.5%) in the 4 mg/kg group, 8 of 16 subjects (50.0%) in the 6 mg/kg group, and 21 of 44 subjects (47.7%) in the 8 mg/kg group. Table 56 shows serious adverse events occurring in ≥3% of subjects.

Table 56. Serious adverse events occurring in ≥3% of subjects

PT (MedDRA ver.23.0)	Number of subjects (%)					
	4 mg/kg N = 21		6 mg/kg N = 16		8 mg/kg N = 44	
	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out
All adverse events	2 (9.5)	1 (4.8)	8 (50.0)	3 (18.8)	21 (47.7)	10 (22.7)
Pneumonitis	1 (4.8)	1 (4.8)	1 (6.3)	1 (6.3)	1 (2.3)	1 (2.3)
Muscular weakness	1 (4.8)	0	0	0	0	0
Seizure	1 (4.8)	0	0	0	0	0
Pneumonia	0	0	1 (6.3)	0	4 (9.1)	2 (4.5)
Infusion related reaction	0	0	1 (6.3)	1 (6.3)	1 (2.3)	1 (2.3)
Ulcerative keratitis	0	0	1 (6.3)	1 (6.3)	1 (2.3)	1 (2.3)
Death	0	0	1 (6.3)	0	0	0
Neck pain	0	0	1 (6.3)	0	0	0
Pneumothorax	0	0	1 (6.3)	0	0	0
Thrombophlebitis septic	0	0	1 (6.3)	0	0	0
Dyspnoea	0	0	0	0	3 (6.8)	1 (2.3)
Hypercalcaemia	0	0	0	0	2 (4.5)	0

Adverse events leading to treatment discontinuation of the study drug occurred in 4 of 21 subjects (19.0%) in the 4 mg/kg group, 3 of 16 subjects (18.8%) in the 6 mg/kg group, and 10 of 44 subjects (22.7%) in the 8 mg/kg group. Table 57 shows the adverse events leading to treatment discontinuation of the study drug.

Table 57. Adverse events leading to treatment discontinuation of the study drug

PT (MedDRA ver.23.0)	Number of subjects (%)					
	4 mg/kg N = 21		6 mg/kg N = 16		8 mg/kg N = 44	
	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug could not be ruled out
All adverse events	4 (19.0)	4 (19.0)	3 (18.8)	2 (12.5)	10 (22.7)	9 (20.5)
Pneumonitis	3 (14.3)	3 (14.3)	0	0	5 (11.4)	5 (11.4)
Ejection fraction decreased	1 (4.8)	1 (4.8)	0	0	0	0
Ulcerative keratitis	0	0	1 (6.3)	1 (6.3)	1 (2.3)	1 (2.3)
Neck pain	0	0	1 (6.3)	0	0	0
Infusion related reaction	0	0	1 (6.3)	1 (6.3)	0	0
Dry eye	0	0	0	0	1 (2.3)	1 (2.3)
Interstitial lung disease	0	0	0	0	1 (2.3)	1 (2.3)
Intraventricular haemorrhage	0	0	0	0	1 (2.3)	0
Pneumonia	0	0	0	0	1 (2.3)	1 (2.3)

7.2.1.2.2 Breast cancer cohort

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in all subjects.

Table 58 shows adverse events occurring in ≥20% of subjects.

Table 58. Adverse events occurring in ≥20% of subjects

SOC PT (MedDRA ver.25.0)	Number of subjects (%) N = 41	
	All Grades	Grade ≥3
All adverse events	41 (100)	17 (41.5)
Nervous system disorders		
Headache	12 (29.3)	0
Eye disorders		
Dry eye	10 (24.4)	0
Gastrointestinal disorders		
Stomatitis	34 (82.9)	4 (9.8)
Nausea	23 (56.1)	0
Constipation	11 (26.8)	0
Vomiting	10 (24.4)	0
Skin and subcutaneous tissue disorders		
Alopecia	15 (36.6)	0
General disorders and administration site conditions		
Fatigue	19 (46.3)	1 (2.4)

Serious adverse events occurred in 6 of 41 subjects (14.6%). Table 59 shows the reported serious adverse events.

Table 59. Reported serious adverse events

PT (MedDRA ver.25.0)	Number of subjects (%) N = 41	
	All adverse events	Adverse events for which a causal relationship to datopotamab deruxtecan could not be ruled out
All adverse events	6 (14.6)	1 (2.4)
Dyspnoea	1 (2.4)	0
Fall	1 (2.4)	0
Hydronephrosis	1 (2.4)	0
Neck pain	1 (2.4)	0
Pneumonia	1 (2.4)	0
Pneumonitis	1 (2.4)	1 (2.4)
Sepsis	1 (2.4)	0
Supraventricular tachycardia	1 (2.4)	0
Biliary obstruction	1 (2.4)	0

Adverse events leading to treatment discontinuation of the study drug occurred in 5 of 41 subjects (12.2%). Table 60 shows the reported adverse events leading to treatment discontinuation of the study drug.

Table 60. Reported adverse events leading to treatment discontinuation of the study drug

PT (MedDRA ver.25.0)	Number of subjects (%) N = 41	
	All adverse events	Adverse events for which a causal relationship to datopotamab deruxtecan could not be ruled out
All adverse events	5 (12.2)	5 (12.2)
Pneumonitis	2 (4.9)	2 (4.9)
Keratitis	1 (2.4)	1 (2.4)
Keratopathy	1 (2.4)	1 (2.4)
Stomatitis	1 (2.4)	1 (2.4)

7.2.2 Global phase III study (Study TB01)

Adverse events occurred in 350 of 360 subjects (97.2%) in the datopotamab deruxtecan group and 337 of 351 subjects (96.0%) in the ICC group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 337 of 360 subjects (93.6%) in the datopotamab deruxtecan group and 337 of 351 subjects (96.0%) in the ICC group. Serious adverse events occurred in 54 of 360 subjects (15.0%) in the datopotamab deruxtecan group and 64 of 351 subjects (18.2%) in the ICC group. Adverse events leading to treatment discontinuation of the study drug occurred in 11 of 360 subjects (3.1%) in the datopotamab deruxtecan group and 10 of 351 subjects (2.8%) in the ICC group [see Table 32 for serious adverse events and adverse events leading to treatment discontinuation of the study drug that occurred at a specified incidence or higher in the datopotamab deruxtecan group].

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.3-7) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that datopotamab deruxtecan has efficacy in the treatment of patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy, and that datopotamab deruxtecan has acceptable safety in view of its benefits. Datopotamab deruxtecan, a drug with a new active ingredient, binds to TROP-2 expressed on the cell membrane of tumor cells, undergoes internalization followed by linker hydrolysis. Released free DXd is considered to cause DNA damage, etc., thereby exerting antitumor effects. Therefore, the drug is clinically meaningful as a treatment option for patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy. PMDA considers that the clinical positioning of datopotamab deruxtecan is subject to further discussion.

PMDA has concluded that datopotamab deruxtecan may be approved if datopotamab deruxtecan is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 22, 2024

Product Submitted for Approval

Brand Name	Datroway for Intravenous Infusion 100 mg
Non-proprietary Name	Datopotamab Deruxtecan (Genetical Recombination)
Applicant	Daiichi Sankyo Company, Ltd.
Date of Application	March 14, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

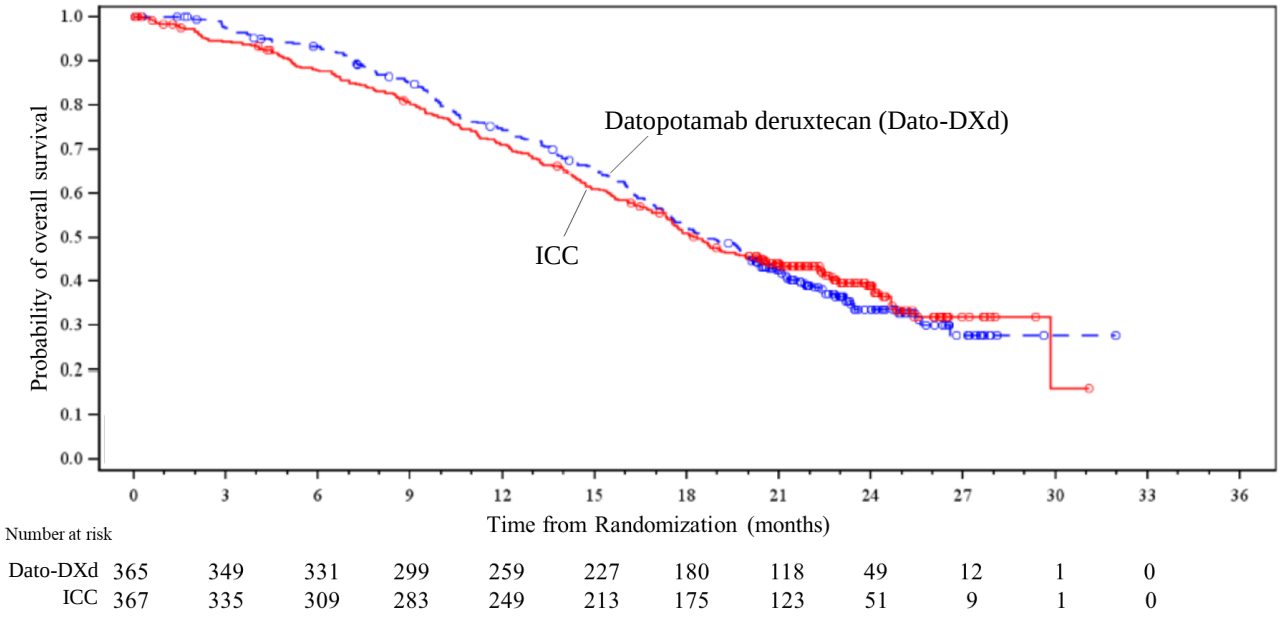
As a result of the discussions presented in Section "7.R.2 Efficacy" in Review Report (1), PFS assessed by BICR according to RECIST ver.1.1, one of the primary endpoints in Study TB01, a global phase III study in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who received prior chemotherapy, demonstrated the superiority of datopotamab deruxtecan over ICC, with its clinically significant effect. Thus, PMDA has concluded that the efficacy of datopotamab deruxtecan had been demonstrated in this patient population.

After the Review Report (1) was finalized, the applicant presented the results of the final OS analysis (Table 61) and the Kaplan-Meier plot (Figure 7) for Study TB01 (data cut-off on [redacted], 20[redacted]). The results did not show clear trends toward shortened OS in the datopotamab deruxtecan group compared to those in the ICC group. PMDA has concluded that the reasons for the failure of final analysis to show a statistically significant OS prolongation in the datopotamab deruxtecan group compared to those in the ICC group need to be further discussed, although the conclusion in Review Report (1) does not need to be changed.

Table 61. The final analysis results for OS (FAS, data cut-off on [redacted])

	Datopotamab deruxtecan	ICC
Number of subjects	365	367
Number of events (%)	223 (61.1)	213 (58.0)
Median [95% CI] (months)	18.6 [17.3, 20.1]	18.3 [17.3, 20.5]
Hazard ratio [95% CI][*1]	1.01 [0.83, 1.22][*2]	
P-value (two-sided)[*3]	0.9445	

*1, A stratified Cox proportional hazard model with prior lines of chemotherapy (1, 2) and geographic region (US/Canada/Europe, other regions) as stratification factors; *2, 95.97% CI corresponding to the significance level was [0.83, 1.23]; *3, using a stratified log-rank test (the stratification factors are the same as those for the stratified Cox proportional hazard model), significance level (two-sided), 0.0403



Number at risk

Dato-DXd	365	349	331	299	259	227	180	118	49	12	1	0
ICC	367	335	309	283	249	213	175	123	51	9	1	0

Figure 7. Kaplan-Meier plot of OS at the final analysis (FAS, data cut-off on [redacted])

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

PMDA asked the applicant to explain the reasons for not achieving statistically significant OS prolongation, one of the primary endpoints for Study TB01, in the datopotamab deruxtecan group compared to the ICC group in the final analysis.

The applicant's explanation:

In the FAS of Study TB01, 73.7% (269 of 365) of subjects in the datopotamab deruxtecan group and 78.7% (289 of 367) of subjects in the ICC group received subsequent therapy; and 12.3% (45 of 365) of subjects in the datopotamab deruxtecan group and 24.0% (88 of 367) of subjects in the ICC group received subsequent ADC therapy. The result of a post-hoc sensitivity analysis, in which patients were censored at the start of subsequent therapy or subsequent ADC therapy, showed that the OS hazard ratio [95% CI] for datopotamab deruxtecan to ICC was 0.66 [0.43, 1.00] for the subsequent therapy and 0.84 [0.69, 1.04] for the subsequent ADC therapy, suggesting that subsequent therapies may have affected the OS results.

Furthermore, patient background factors[53] with a datopotamab deruxtecan to ICC hazard ratio of >1 identified by a patient background factor-based subgroup analysis were subjected to an analysis that took into account the imbalance distribution between treatment groups. The results did not differ markedly from the results of the analysis regardless of the imbalance. Therefore, it is unlikely that the imbalance distribution of patient background factors between treatment groups affected the OS results.

PMDA accepted the applicant's explanation.

1.2 Safety

PMDA's view:

Based on the discussions in Section "7.R.3 Safety" in Review Report (1), corneal disorder, ILD, infusion-related reactions, and myelosuppression are adverse events that require particular attention during the treatment with datopotamab deruxtecan.

While the use of datopotamab deruxtecan requires particular attention to these adverse events, patients should be able to tolerate the treatment under appropriate monitoring, adverse event management, and dose interruption, etc. by a physician with sufficient knowledge and experience in cancer chemotherapy.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indication

In view of the discussions in Section "7.R.4 Clinical positioning and indication" in Review Report (1), PMDA concluded that the indication of datopotamab deruxtecan and the precautions concerning indication should be specified as in the table below.

Indication	Precautions concerning indication
Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy	• Datopotamab deruxtecan should be administered to patients who received prior anthracycline- or taxane-based chemotherapy. • Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the "Clinical studies" section, and the efficacy and safety of datopotamab deruxtecan. • The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

Based on the above, PMDA instructed the applicant to set the indication and the precautions concerning indications as shown above, and the applicant agreed with the instruction.

[53] Patient background factors: (1) number of lines of prior chemotherapy, 1; (2) geographic region, "rest of world" (other than US/Canada/Europe); (3) prior use of CDK4/6 inhibitor, yes; (4) duration of CDK4/6 inhibitor use in previous treatment, ≤12 months; (5) prior use of taxane- or anthracycline-based chemotherapy, taxane-based regimen only; (6) prior taxane- or anthracycline-based chemotherapy, anthracycline-based regimen only; (7) prior taxane- or anthracycline-based chemotherapy, both regimens; (8) age at randomization, ≥65 years; (9) race, Asian; (10) prespecified ICC agent, capecitabine; (11) prespecified ICC agent, gemcitabine; (12) brain metastases, no; (13) sex, female; (14) HER2 status, IHC 1+, or IHC 2+/ISH−; (15) ECOG performance status, 1; (16) time from the completion of (neo) adjuvant therapy to the initiation of chemotherapy for unresectable or recurrent breast cancer, ≥12 months.

1.4 Dosage and administration

In view of the discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA has concluded that the dosage and administration of datopotamab deruxtecan and the precautions concerning dosage and administration should be set as follows.

Dosage and Administration

The usual adult dosage is 6 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of datopotamab deruxtecan have not been established in its combination use with other antineoplastic agents.
- To reduce infusion reactions, prophylactic antihistamine and antipyretic-analgesic should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary.
- If an adverse reaction to datopotamab deruxtecan occurs, the dose must be interrupted, reduced, or the treatment must be discontinued based on the following criteria.

Dose level for reductions

First dose reduction	4 mg/kg
Second dose reduction	3 mg/kg
Third dose reduction	Discontinue treatment

Criteria for dose interruption, reduction, or treatment discontinuation after adverse drug reactions

Adverse reaction	Severity[Note)]	Action
ILD	Grade 1	Interrupt the dose until complete resolution. Treatment may be resumed at the same dose level after ≤28 day interruption, or at 1 lower dose level after >28 day interruption.
	Grade 2, 3, or 4	Discontinue treatment.
Keratitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level. For recurrence, interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.
Infusion-related reaction	Grade 1	Reduce infusion rate by 50%. If no new infusion-related reaction develops, the next infusion may be administered at the rate at event onset.
	Grade 2	Interrupt infusion. After resolution to Grade ≤1, infusion may be resumed at the infusion rate reduced by 50%. Administer the next infusion at the rate reduced by 50% from that at event onset. If no new infusion-related reaction develops, the subsequent infusions may be administered at the rate at event onset.
	Grade 3 or 4	Discontinue treatment.
Neutrophil count decreased, white blood cell count decreased, anaemia	Grade 3	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same or 1 lower dose level.
Platelet count decreased	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
Other adverse drug reactions	Grade 3	Interrupt the dose until resolution to Grade ≤1 or baseline. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.

Note) According to the NCI-CTCAE ver.5.0.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

Accordingly, PMDA instructed the applicant to define the dosage and administration and offer advice in the "Precautions Concerning Dosage and Administration" section as above, and the applicant agreed with the instruction.

1.5 RMP (draft) and post-marketing investigations

In view of the discussions in Section "7.R.6 Risk management plan (draft)" in Review Report (1), PMDA concluded that the safety specification for the RMP (draft) should include the items shown in Table 62.

Table 62. Safety and efficacy specifications in the RMP (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Corneal disorder • ILD • Infusion-related reactions • Myelosuppression	• Embryo-fetal toxicity • Severe diarrhea/enterocolitis • Intestinal perforation, gastrointestinal hemorrhage, intestinal obstruction • Anaphylaxis • Hepatic dysfunction • Renal dysfunction • Thromboembolism • Cardiac disorders	None
Efficacy specification		
None		

In view of the discussions in Section "7.R.7 Post-marketing investigations" in Review Report (1), post-marketing surveillance needs not be conducted immediately after approval to investigate the safety, etc. of datopotamab deruxtecan in patients with unresectable or recurrent HR-positive, HER2-negative breast cancer who have received prior chemotherapy, where the provision of information to medical settings about adverse events of datopotamab deruxtecan of particular attention (corneal disorder, ILD, infusion-related reactions, and myelosuppression), collection of datopotamab deruxtecan safety information, and implementation of appropriate safety measures based on current and future information are ensured through early post-marketing phase vigilance and routine pharmacovigilance activities.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above and made the following comment.

- Corneal disorder is an adverse event characteristic of datopotamab deruxtecan, and its underlying mechanism remains unclear. The applicant should continue gathering data pertaining to the mechanism of the corneal disorder caused by datopotamab deruxtecan.

In response, PMDA has concluded that the RMP (draft) for datopotamab deruxtecan should include the safety specification presented in Table 62, and that additional risk minimization activities should be implemented as presented in Table 63.

Table 63. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance	None	• Disseminate data gathered through early post-marketing phase vigilance • Organize and disseminate information materials for healthcare professionals • Organize and disseminate information materials for patients

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration presented below with the following approval condition, only where appropriate cautionary advice is offered via the package insert, proper use-related information is provided in the post-marketing settings, and proper use of the product is adhered to at medical institutions

adequately prepared for emergency care and under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy. Datopotamab deruxtecan is a drug with a new active ingredient, thus the re-examination period is 8 years. It is classified as a biological product. The drug substance and drug product are both classified as powerful drugs. its proper use is assured with

Indication

Patients with unresectable or recurrent hormone receptor-positive, HER2-negative breast cancer who have received prior chemotherapy

Dosage and Administration

The usual adult dosage is 6 mg/kg (body weight) of datopotamab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is tolerated, the subsequent infusions may be administered over 30 minutes. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warnings

1. Datopotamab deruxtecan should be administered only to patients who are considered eligible for its use, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy and at medical institutions adequately prepared for emergency care. Prior to the treatment, the efficacy and risks associated with datopotamab deruxtecan should be thoroughly explained to the patient and/or the family, and consent must be obtained.
2. In light of reported deaths from interstitial lung disease that developed after the administration of datopotamab deruxtecan, datopotamab deruxtecan should be used in coordination with physicians with expertise in respiratory illnesses. During treatment, patients should be closely monitored for initial symptoms (e.g., dyspnea, cough, and pyrexia), have regular measurement of arterial oxygen saturation (SpO_2) and chest X-ray, chest CT, etc. In the event of an abnormality, the patient should discontinue datopotamab deruxtecan and be appropriately treated with corticosteroids, etc.
3. Prior to the start of datopotamab deruxtecan treatment, patient eligibility should be carefully determined based on chest CT and patient interview to confirm that the patient has no current or history of interstitial lung disease.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients of the product.

Precautions Concerning Indication

1. Datopotamab deruxtecan should be administered to patients who received prior anthracycline- or taxane-based chemotherapy.

2. Patient eligibility should be determined based on a thorough understanding of prior treatment of clinical study participants, etc., as mentioned in the “Clinical studies” section, and the efficacy and safety of datopotamab deruxtecan.
3. The efficacy and safety of datopotamab deruxtecan as a neoadjuvant or adjuvant therapy has not been established.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of datopotamab deruxtecan have not been established in its combination use with other antineoplastic agents.
2. To reduce infusion-related reactions, prophylactic antihistamine and antipyretic-analgesic should be administered before datopotamab deruxtecan. The use of prophylactic adrenal corticosteroids should also be considered as necessary.
3. If an adverse reaction to datopotamab deruxtecan occurs, the dose must be interrupted, reduced, or the treatment must be discontinued based on the following criteria.

Dose level for reductions

First dose reduction	4 mg/kg
Second dose reduction	3 mg/kg
Third dose reduction	Discontinue treatment

Criteria for dose interruption, reduction, or treatment discontinuation after adverse drug reactions

Adverse reaction	Severity[Note)]	Action
Interstitial lung disease (ILD)	Grade 1	Interrupt the dose until complete resolution. Treatment may be resumed at the same dose level after ≤28 day interruption, or at 1 lower dose level after >28 day interruption.
	Grade 2, 3, or 4	Discontinue treatment.
Keratitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same dose level. For recurrence, interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.
Infusion-related reaction	Grade 1	Reduce infusion rate by 50%. If no new infusion-related reaction develops, the next infusion may be administered at the rate at event onset.
	Grade 2	Interrupt infusion. After resolution to Grade ≤1, infusion may be resumed at the infusion rate reduced by 50%. Administer the next infusion at the rate reduced by 50% from that at event onset. If no new infusion-related reaction develops, the subsequent infusions may be administered at the rate at event onset.
	Grade 3 or 4	Discontinue treatment.
Neutrophil count decreased, white blood cell count decreased, anemia	Grade 3	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤2. Treatment may be resumed at the same or 1 lower dose level.
Platelet count decreased	Grade 3	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Interrupt the dose until resolution to Grade ≤1. Treatment may be resumed at 1 lower dose level.
Other adverse drug reactions	Grade 3	Interrupt the dose until resolution to Grade ≤1 or baseline. Treatment may be resumed at the same or 1 lower dose level.
	Grade 4	Discontinue treatment.

Note) Accordance to the NCI-CTCAE ver.5.0.

Appendix

List of Abbreviations

A/G ratio	albumin/globulin ratio
ADC	antibody-drug conjugate
ADCC	antibody dependent cellular cytotoxicity
ALT	alanine aminotransferase
application	application for marketing approval
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{21day}	AUC from time zero to 21 days
AUC_{inf}	AUC from time zero to infinity
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	bis in die
BSA	bovine serum albumin
C_0	initial plasma concentration
C1q	complement component 1q
C_{avg}	average concentration
CDC	complement dependent cytotoxicity
CDK4/6	cyclin dependent kinase 4 and 6
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CEX-HPLC	cation exchange high performance liquid chromatography
CHK1	checkpoint kinase 1
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
CL	total body clearance
Clinical Practice Guidelines for Breast Cancer in Japan	The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer
CL_{lin}	linear clearance
C_{max}	maximum concentration
COVID-19	coronavirus disease
CQA	critical quality attribute
CrCL	creatinine clearance
CYP	cytochrome P450
Dato	Datopotamab
datopotamab deruxtecan	datopotamab deruxtecan (genetical recombination)
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DXd	MAAA-1181a
ECL	electro-chemiluminescence
ELISA	enzyme-linked immunosorbent assay
eribulin	eribulin mesilate
ESMO	European Society of Medical Oncology
ESMO (ABC 5) Guidelines	5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)
ESMO Clinical Practice Guidelines	ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer
FAS	full analysis set
FcRn	neonatal Fc receptor
FcγR	Fcγ Receptor
gemcitabine	gemcitabine hydrochloride

HCP	host cell protein
[redacted]	[redacted]
HER2	human epidermal growth factor receptor type 2
HI-HPLC	hydrophobic interaction high performance liquid chromatography
HNSTD	highest non-severely toxic dose
HR	hormone receptor
ICC	Investigator's Choice Chemotherapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) Guidelines	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5E Guidelines	"Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" (PFSB/ELD Notification No. 0426001, dated April 26, 2005)
ICH-Q5D Guidelines	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
IFN	Interferon
Ig	immunoglobulin
IgG-DXd	An ADC in which DXd is attached to a humanized IgG1 monoclonal antibody by a linker, which is the same linker used in datopotamab deruxtecan
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IP-10	IFN-γ inducible protein 10
ISH	*in situ* hybridization
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LIVCA	limit of in vitro cell age
MATE	multidrug and toxin extrusion
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MIP	macrophage inflammatory protein
MRP	multidrug resistance associated protein
MS	mass spectrum
MTD	maximum tolerated dose
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OS	overall survival
PALS	periarteriolar lymphoid sheath
PARP	poly (ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cell

PBPK	physiologically based pharmacokinetics
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PT	preferred term
Q3W	quaque 3 weeks
QT	QT interval
QTc	QT interval corrected
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
RP2D	recommended Phase 2 dose
RP-HPLC	reversed-phase-high performance liquid chromatography
SE-HPLC	size exclusion high performance liquid chromatography
SG	sacituzumab govitecan (genetical recombination)
SOC	system organ class
SP-D	surfactant protein D
STD_{10}	severely toxic dose in 10% of the animals
Study J101	Study DS8201-A-J101
Study TB01	Study TROPION-Breast01
Study TL01	Study TROPION-Lung01
Study TL05	Study TROPION-Lung05
Study TP01	Study TROPION-PanTumor01
$t_{1/2}$	terminal elimination half-life
talazoparib	talazoparib tosilate
T-DXd	trastuzumab deruxtecan (genetical recombination)
t_{max}	time to reach the maximum concentration
TNF	tumor necrosis factor
total anti-TROP-2 antibody	total of datopotamab deruxtecan and datopotamab
TROP	trophoblast cell surface antigen
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
Vc	volume of distribution of central compartment
vinorelbine	vinorelbine tartrate
V_{max}	maximum elimination rate
Vp	volume of distribution of peripheral compartment
V_{ss}	volume of distribution at steady state
WCB	working cell bank
ΔQTcF	change from baseline in QT interval corrected with Fridericia's formula