**Report on the Deliberation Results**

March 3, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Enhertu for Intravenous Drip Infusion 100 mg |
| **Non-proprietary Name** | Trastuzumab Deruxtecan (Genetical Recombination) (JAN*) |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | September 9, 2019 |

**Results of Deliberation**

In its meeting held on February 26, 2020, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to provide data on the efficacy and safety of the product from the ongoing phase III study in patients with unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy to healthcare professionals in an appropriate manner.
3. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been collected. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.

**Japanese Accepted Name (modified INN)*

**Review Report**

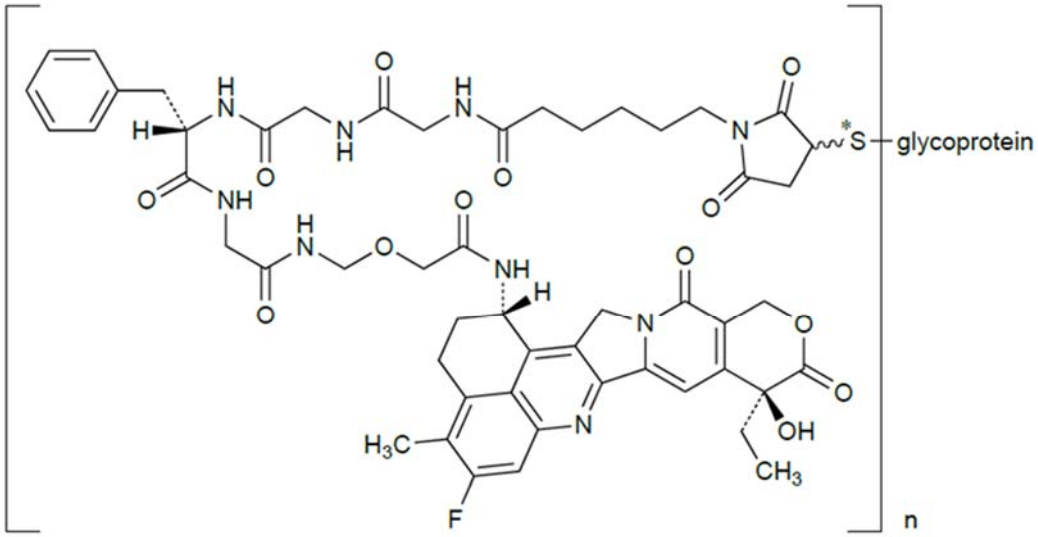
February 17, 2020
Pharmaceuticals and Medical Devices Agency

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** | Enhertu for Intravenous Drip Infusion 100 mg |
| **Non-proprietary Name** | Trastuzumab Deruxtecan (Genetical Recombination) |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | September 9, 2019 |
| **Dosage Form/Strength** | Injection: each vial contains 107 mg of trastuzumab deruxtecan (genetical recombination) |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |
| **Definition** | Trastuzumab Deruxtecan is an antibody-drug-conjugate (molecular weight: ca. 157,000) 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 a camptothecin derivative and a linker, attached to an average of 8 Cys residues of a recombinant monoclonal antibody.<br>The monoclonal antibody moiety is a humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human epidermal growth factor receptor type 2 (HER2) monoclonal antibody and framework regions and constant regions from human IgG1 and produced in Chinese hamster ovary cells. The protein moiety is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 450 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each. |

**Structure**

Structural formula of deruxtecan site:




n = approximately 8

* A sulfur atom of a Cys residue of the monoclonal antibody moiety

Amino acid sequence:

L-chain:

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS

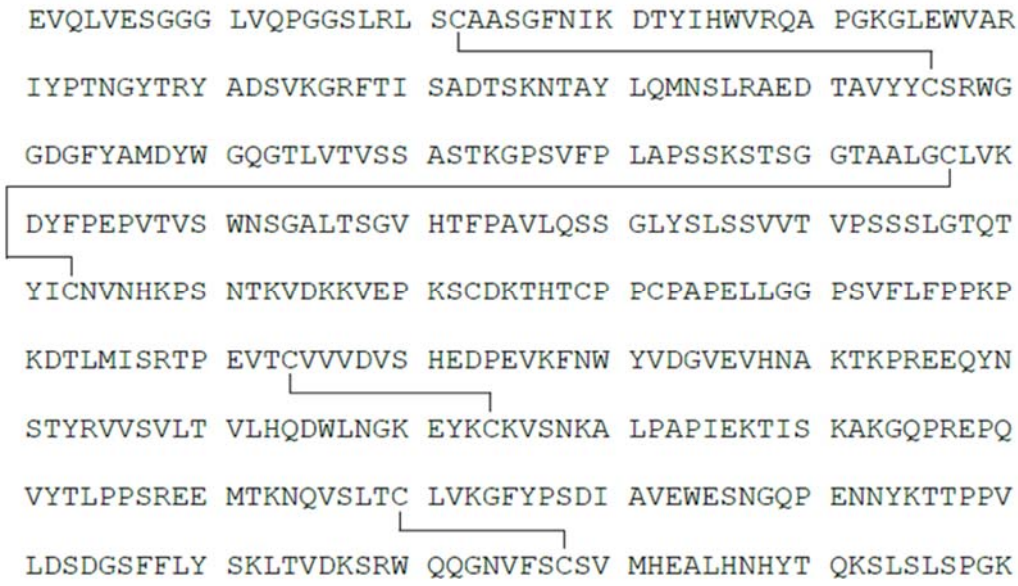
ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ

GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

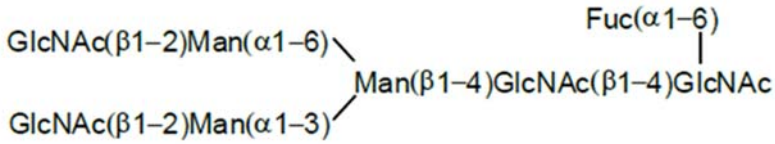
LSSPVTKSFN RGEC

H-chain:




| | |
|---|---|
| Intra-chain disulfide bonds: | solid lines |
| Inter-chain disulfide bonds: | L-chain C214-H-chain C223, H-chain C229-H-chain C229, H-chain C232-H-chain C232 |
| Pyroglutamic acid (partial): | H-chain E1 |
| Potential drug binding sites: | L-chain C214, H-chain C223, H-chain C229, H-chain C232 |
| Glycosylation: | H-chain N300 |
| Partial processing: | H-chain K450 |

Main proposed carbohydrate structure:




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

| | |
|---|---|
| Molecular formula: | $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$ (protein moiety) |
| Molecular weight: | approximately 157,000 |

**Items Warranting Special Mention**

Conditional Early Approval System (PSEHB/PED Notification No. 1202-2 dated December 2, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

**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 unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy where no other standard of care treatment option is available, 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 conditions. The risk factors for interstitial lung disease should be further evaluated in the post-marketing surveillance.

**Indication**

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

**Dosage and Administration**

The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to provide data on the efficacy and safety of the product from the ongoing phase III study in patients with unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy to healthcare professionals in an appropriate manner.
3. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been collected. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.

**Attachment**

# Review Report (1)

January 10, 2020

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** | Enhertu for Intravenous Drip Infusion 100 mg |
| **Non-proprietary Name** | Trastuzumab Deruxtecan (Genetical Recombination) |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | September 9, 2019 |
| **Dosage Form/Strength** | Injection: each vial contains 107 mg of trastuzumab deruxtecan (genetical recombination) |
| **Proposed Indication** | Unresectable or recurrent HER2-positive breast cancer previously treated with trastuzumab emtansine (genetical recombination) |

**Proposed Dosage and Administration**

The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion every 3 weeks.

**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

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) discovered by the applicant and consists of MAAL-9001, a humanized monoclonal antibody of immunoglobin G1 (IgG1) subclass targeting human epidermal growth factor receptor type 2 (HER2), that is bound via a peptide linker to MAAA-1181a, a topoisomerase I inhibitor derivative of exatecan. Trastuzumab deruxtecan binds to HER2 expressed on the tumor cell membrane. Upon internalization into the cell, the linker undergoes hydrolysis, releasing MAAA-1181a. The released MAAA-1181a is thought to induce deoxyribonucleic acid (DNA) damage, apoptosis, and other effects, leading to inhibition of tumor growth.

### 1.2 Development history etc.

Study J101 was a global phase I study conducted by the applicant from September 2015 in patients with unresectable or recurrent HER2-positive breast cancer, etc. From October 2017, a global phase II study (Study U201) was conducted by the applicant in patients with unresectable or recurrent HER2-positive breast cancer previously treated with trastuzumab emtansine (genetical recombination) (T-DM1).

In the US, an application for trastuzumab deruxtecan was filed in August 2019, using the results of the pivotal Study U201, and accelerated approval was granted in December 2019 for the following indication: “ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received ≥2 prior anti-HER2-based regimens in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”

As of December 2019, trastuzumab deruxtecan has been approved only in the US for the corresponding indication of unresectable or recurrent HER2-positive breast cancer.

In Japan, enrollment of patients in Studies J101 and U201 began in September 2015 and October 2017, respectively.

Recently, an application for marketing approval of trastuzumab deruxtecan has been filed, using the results from Study U201 as a pivotal study.

Trastuzumab deruxtecan has been designated as a product to which the conditional early approval system applies (PSEHB/PED Notification No. 1202-2 dated December 2, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Trastuzumab deruxtecan is an ADC that consists of anti-HER2 monoclonal antibody (MAAL-9001) that is bound at the inter-chain disulfide position to a topoisomerase I inhibitor derivative of exatecan (MAAA-1181a) via a peptide drug-linker (MAAA-1162a). The amino acid sequence of the antibody MAAL-9001 is the same as that of trastuzumab except that lysine residues at the heavy chain C-terminal remain in MAAL-9001.

### 2.1 Drug substance

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

#### 2.1.1 MAAL-9001

##### 2.1.1.1 Generation and control of cell substrate

The expression construct of MAAL-9001 was created based on the amino acid sequence of trastuzumab. The construct was transfected into a Chinese hamster ovary (CHO) cell line, and from the transfected cells, a master cell bank (MCB) and a working cell bank (WCB) were prepared based on a clone optimal for the production of MAAL-9001.

Characterization and purity testing were conducted for the MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) in accordance with the 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 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 MAAL-9001 consists of the following steps: thawing of WCB/expansion culture, preculture, production culture, harvesting, [redacted] chromatography, [redacted] viral inactivation/[redacted], [redacted] chromatography, [redacted] chromatography, [redacted], virus removal filtration, and final filtration/filling/testing/freezing/storage.

Critical steps are [redacted], [redacted] viral inactivation/[redacted], [redacted] chromatography, [redacted] chromatography, and virus removal filtration.

Process validation is performed on a commercial scale for the manufacturing process of MAAL-9001.

#### 2.1.1.3 Safety evaluation of adventitious agents

With the exception of CHO cell lines, the host cells, no raw materials of biological origin are used in the process to manufacture MAAL-9001.

Purity was tested on the MCB, WCB, and CAL [see Section 2.1.1.1]. Bioburden testing, mycoplasma testing, *in vitro* adventitious virus testing, and transmission electron microscopy were performed on pre-harvest unprocessed bulk produced at commercial scale. None of the tests revealed contamination with viral or non-viral adventitious agents. The bioburden testing, mycoplasma testing, and *in vitro* adventitious virus testing on pre-harvest unprocessed bulk 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 studies**

| Manufacturing process | Virus reduction factor ($log_{10}$) | | | |
|---|---|---|---|---|
| | Xenotropic murine leukemia virus | Minute virus of mice | Reovirus type 3 | Pseudorabies virus |
| [redacted] viral inactivation | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus removal filtration | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall reduction factor | ≥15.96 | ≥10.24 | ≥12.38 | ≥16.71 |

#### 2.1.1.4 Manufacturing process development

The major changes to the manufacturing process during the development of MAAL-9001 include changes in [redacted], [redacted], [redacted], [redacted], and [redacted] (the manufacturing process before the changes and after the changes are referred to as MAb Process-1 and MAb Process-2 [proposed manufacturing process], respectively). The formulations produced from the drug substances derived from MAb Process-1 were used in the initial development phase (Study J101, except for Part 2e), while those produced from the drug substances derived from MAb Process-2 were used in the rest of the clinical studies. When the manufacturing processes were changed, comparability was evaluated in terms of the quality attributes. While similarity was not confirmed for some quality attributes, the comparability of MAAL-9001 has been confirmed, taking account of the results from the comparability evaluation of the ADC drug substance before and after the manufacturing process change [see Section 2.1.3.2].

The manufacturing process was developed using a quality by design (QbD) approach [see Section 2.3].

#### 2.1.1.5 Characterization

##### 2.1.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed for MAAL-9001.

**Table 2. Evaluation items for characterization of MAAL-9001**

| | |
|---|---|
| Primary/higher order structure | Amino acid sequence, N- and C-terminal amino acid sequences, post-translational modifications (deamidation, oxidation, isomerization, glycation), disulfide bonds, [redacted], secondary structure, [redacted], thermal stability |
| Physicochemical properties | Molecular weight, charge variants, size variants, extinction coefficient |
| Carbohydrate structure | N-linked glycosylation site, [redacted], N-linked glycan profile, O-linked glycan profile |
| Biological properties | HER2 binding activity |
| | Binding activities for FcγR IIIa, FcRn, and C1q |
| | Cell growth inhibitory activity (*in vitro* and *in vivo*) |
| | ADCC activity |

The biological properties of MAAL-9001 were compared with those of the drug substance [see Section 2.1.3.3.1]. The results indicated that MAAL-9001 has binding activity to HER2, cell growth inhibitory activity, and antibody dependent cellular cytotoxicity (ADCC) activity.

#### 2.1.1.5.2 Product-related substances/Product-related impurities

On the basis of the results of characterization in Section "2.1.1.5.1 Structure and characterization," Compound A's were identified as product-related substances, and Impurity A, Impurity B, and Impurity C as product-related impurities. The product-related impurities are adequately controlled by the specifications for MAAL-9001, the drug substance, and the drug product.

#### 2.1.1.5.3 Process-related impurities

Process-related impurities were defined as host cell proteins (HCPs), host cell DNA, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, elemental impurities, and extractables/leachables. All process-related impurities have been confirmed to be adequately removed during the manufacturing process.

### 2.1.1.6 Control of MAAL-9001

The proposed specifications for MAAL-9001 include content, description, identification ([redacted] high-pressure liquid chromatography [HPLC]), pH, [redacted], purity ([redacted] HPLC, size exclusion-high-pressure liquid chromatography [SE-HPLC], [redacted], and [redacted]), bacterial endotoxins, microbial limits, HER2 binding activity, and assay (ultraviolet-visible spectrophotometry).

### 2.1.1.7 Stability of MAAL-9001

Table 3 shows main stability studies for MAAL-9001.

**Table 3. Summary of main stability studies for MAAL-9001**

| | Number of batches[*1] | Storage condition | Study period | Container |
|---|---|---|---|---|
| Long-term | 7 | [redacted]°C | [redacted] months[*2] | [redacted] |
| Accelerated | 7 | 5 ± 3°C | 6 months | |
| Stress | 7 | 25 ± 2°C/60 ± 5% RH | 6 months | |

*1, The batches were produced by the proposed manufacturing process; *2, 3 batches were tested for [redacted] months, 4 batches for [redacted] months, and the stability testing is ongoing up to [redacted] months.

The long-term and accelerated tests showed no clear changes in quality attributes throughout the testing period.

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

On the basis of the above results, a shelf life of [redacted] months was proposed for MAAL-9001 when stored at [redacted] °C using [redacted].

### 2.1.2 MAAA-1162a

#### 2.1.2.1 Characterization

MAAA-1162a, which consists of a peptide linker and an exatecan derivative, is a white to light yellow-white solid. Its description, melting point, hygroscopicity, solubility, and crystalline properties have been determined.

The chemical structure of MAAA-1162a has been elucidated by elemental analysis, infrared absorption spectrum (IR), $^{1}H$- and $^{13}C$-nuclear magnetic resonance spectrum (NMR), single crystal X-ray structure analysis,[1)] and mass spectrometry. MAAA-1162a has 3 chiral centers and is composed of a single stereoisomer.

#### 2.1.2.2 Manufacturing process

MAAA-1162a is synthesized using the following 4 starting materials:

(a) [redacted]
(b) [redacted]
(c) [redacted]
(d) [redacted]

Using the QbD approach, quality control strategies have been established based on identification of critical quality attributes (CQAs) and other evaluations (Table 4).

**Table 4. Outline of control strategies for MAAA-1162a**

| CQA | Control method |
|---|---|
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted] |

1) [redacted] were analyzed to identify the stereochemistry.

[redacted] step for [redacted] has been defined as a critical step, and process control items and values have been established. During the review process, process control items and values were established for the synthetic processes of Intermediate [redacted],[2] [redacted],[3] [redacted],[4] and [redacted].

### 2.1.2.3 Control of MAAA-1162a

The proposed specifications for MAAA-1162a include content, description, identification (IR and liquid chromatography [LC]), optical rotation, purity (related substances [LC] and residual solvents [gas chromatography (GC)]), and assay (LC). The identification (LC) was defined during the review process.

### 2.1.2.4 Stability of MAAA-1162a

Table 5 shows main stability studies for MAAA-1162a. Photostability testing demonstrated that MAAA-1162a is photo[redacted].

**Table 5. Summary of main stability studies for MAAA-1162a**

| Study | Number of batches (scale) | Temperature | Humidity | Container | Storage period |
|---|---|---|---|---|---|
| Long-term | 1 (commercial scale) | [redacted]°C | [redacted]%RH | [redacted] + [redacted][5] | 12 months |
| Accelerated | 2 (pilot scale) | [redacted]°C | [redacted]%RH | | 6 months |

On the basis of the above results, a retest period of [redacted] months has been proposed for MAAA-1162a when placed in [redacted] with [redacted],[5] packaged in [redacted], placed in [redacted], and stored at [redacted], by referring to ICH Q1E Guidelines. Long-term testing will be continued for up to 60 months.

### 2.1.3 Trastuzumab deruxtecan (genetical recombination)

### 2.1.3.1 Manufacturing process

The manufacturing process for the drug substance consists of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and filling/testing/freezing/storage. [redacted], [redacted], [redacted], [redacted], and [redacted] steps have been defined as critical steps.

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

2) [redacted]

3) [redacted]

4) [redacted]

5) [redacted]

### 2.1.3.2 Manufacturing process development

The major changes to the manufacturing process during the development of the drug substance are as follows (the manufacturing processes are referred to as Processes A, B, and C, and the proposed manufacturing process):

- From Process A to Process B: Changes including [redacted], [redacted], [redacted], and [redacted]
- From Process B to Process C: Changes including [redacted] and [redacted]
- From Process C to the proposed manufacturing process: Changes including [redacted]

The processes used for the manufacture of formulations in the studies were as follows: Process A in Study J101 (excluding Part 2e); Process B in Study J101 (Part 2e); and Process B and Process C in Studies J102, A104, A103, and U201. The comparability of the drug substances was evaluated before and after the change from Process A to Process B using evaluation of comparability in quality attributes and clinical study data[6)]. In addition, the comparability of the drug substances was evaluated before and after the changes from Process B to Process C and Process C to the proposed manufacturing process using evaluation of comparability in quality attributes, and the comparability of drug substances before and after the changes was confirmed.

The manufacturing process was developed using a QbD approach [see Section 2.3].

### 2.1.3.3 Characterization

#### 2.1.3.3.1 Structure and characterization

Table 6 summarizes the characterization performed for the drug substance.

**Table 6. Evaluation items for characterization of the drug substance**

| | |
|---|---|
| Primary/higher order structure | Amino acid sequence, N- and C-terminal amino acid sequences, post-translational modifications (deamidation, oxidation, isomerization, glycation), disulfide bonds, [redacted], drug-to-antibody ratio, [redacted], secondary structure, [redacted], thermal stability |
| Physicochemical properties | Molecular weight, charge variants, size variants |
| Carbohydrate structure | N-linked glycan profile |
| Biological properties | HER2 binding activity |
| | Binding activities for FcγR IIIa, FcRn, and C1q |
| | Cell growth inhibitory activity (*in vitro* and *in vivo*) |
| | ADCC activity, [redacted] activity |

The results of the investigation of biological properties are as shown below. The biological properties of the drug substance were compared with those of the antibody MAAL-9001 in the evaluation.

- The results of enzyme-linked immunosorbent assay (ELISA) confirmed the HER2 binding activity of MAAL-9001 and the drug substance.

6) In a global phase I study (Study J101) conducted in patients with unresectable or recurrent HER2-positive breast cancer, etc. to investigate the PK and other aspects of trastuzumab deruxtecan, the PK parameters were largely similar between trastuzumab deruxtecan including the drug substance manufactured by Process A and Process B [see Section 6.2.1.1].

- The results of [redacted] confirmed the Fc receptor (Fc gamma receptor IIIa [FcγR IIIa] and neonatal Fc receptor [FcRn]) binding activities and C1q binding activity of MAAL-9001 and the drug substance.
- [redacted] activity was investigated using a human lung cancer [redacted] cell line, human breast cancer [redacted] cell line, human gastric cancer [redacted] cell line, and human breast cancer [redacted] cell line. Among all the HER2-positive cell lines tested, MAAL-9001 showed such activity against the [redacted] cell line and [redacted] cell line, whereas the drug substance showed such activity against all HER2-positive cell lines.
- MAAL-9001 and the drug substance showed ADCC activity when evaluated using the [redacted] cell line as target cells, and [redacted] cells or the [redacted] cell line as effector cells.
- The antitumor activity was investigated by inoculating [redacted] cells to nude mice, and the drug substance displayed a more potent antitumor effect compared with MAAL-9001.
- The drug substance did not show [redacted] activity when evaluated using [redacted] and the [redacted] cell line.

#### 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, Compound B's were identified as product-related substances, and Impurity I and Impurity J as product-related impurities. The product-related impurities are adequately controlled by the specifications for the drug substance and drug product.

#### 2.1.3.3.3 Process-related impurities

Impurity K, Impurity L, Impurity M, Impurity N, Impurity O, Impurity P, Impurity Q, Impurity R, Impurity S, Impurity T, Impurity U, Impurity V, and Impurity W, were identified as process-related impurities [see Section 2.1.1.5.3]. All process-related impurities were confirmed to be adequately removed during the manufacturing process.

### 2.1.3.4 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted] and [redacted]), osmolality, pH, purity ([redacted], SE-HPLC, [redacted], [redacted], [redacted], and [redacted]), drug-to-antibody ratio (DAR), bacterial endotoxins, microbial limits, potency (cell growth inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

### 2.1.3.5 Stability of drug substance

Table 7 shows main stability studies for the drug substance.

**Table 7. Summary of main stability studies for the drug substance**

| | Manufacturing process | Number of batches | Storage condition | Study period | Container |
|---|---|---|---|---|---|
| Long-term | Process B | 3 | −20 ± 5°C | [redacted] months*1 | Ethylene-vinyl acetate bag |
| | Proposed manufacturing process | 4 | | [redacted] months*2 | |
| Accelerated | Process B | 3 | 5 ± 3°C | 6 months | |
| | Proposed manufacturing process | 2 | | | |
| Stress | Process B | 3 | 25 ± 2°C/60 ± 5%RH | 6 months | |
| | Proposed manufacturing process | 2 | | | |
| Photostability | Process B | 1 | Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m$^2$, at 25°C | | |

*1, The stability testing is ongoing up to [redacted] months; *2, 2 batches were tested for [redacted] months, the other 2 batches for [redacted] months, and the stability testing is ongoing up to [redacted] months

The long-term and accelerated tests showed no change in quality attributes throughout the testing period.

The results of the stress testing included the following: an increase of [redacted] in [redacted] and an increasing trend of [redacted]; a decrease of [redacted] in [redacted]; an increase of [redacted] and an increasing trend of [redacted]; a decrease of [redacted] in [redacted]; an increase of [redacted] and an increasing trend of [redacted]; a decrease of [redacted] in [redacted]; and an increase of [redacted].

Photostability testing demonstrated that the drug substance is photolabile.

On the basis of the above results, a shelf life of [redacted] months has been proposed for the drug substance when stored at −25°C to −15°C in an ethylene-vinyl acetate bag as primary packaging, and [redacted] as secondary packaging, protected from light.

## 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 107 mg of trastuzumab deruxtecan (protein content). The drug product contains, as excipients, sucrose, L-histidine, L-histidine hydrochloride hydrate, and polysorbate 80. An excess volume of trastuzumab deruxtecan is filled in each vial compared with the labeled amount so that, following reconstitution with 5 mL of water for injection, 100 mg of trastuzumab deruxtecan (the resulting protein concentration is 20 mg/mL) can be obtained.

### 2.2.2 Manufacturing process

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

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

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

### 2.2.3 Manufacturing process development

The major changes to the manufacturing process during the development of the drug product are as follows (the manufacturing processes are referred to as Process 1, Process 2, Process 3, and the proposed manufacturing process):

- From Process 1 to Process 2: Changes in fill volume, [redacted], [redacted], and production scale.
- From Process 2 to Process 3: Changes in dosage form, [redacted], [redacted], manufacturing site, and production scale.
- From Process 3 to the proposed manufacturing process: Changes in manufacturing site and production scale.

The processes used for the manufacture of formulations in the studies were as follows: Process 1 in Study J101 (excluding Part 2e); Process 2 in Studies J101 (Part 2e) and U201 (Parts 1 and 2); and Process 3 in Studies J102, A103, and U201 (Part 2). The comparability of the formulations was evaluated before and after the changes in the manufacturing processes using evaluation of comparability in quality attributes, and the comparability of formulations before and after the changes was confirmed.

The manufacturing process was developed using a QbD approach [see Section 2.3].

### 2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description (appearance and after reconstitution), identification ([redacted] and [redacted]), osmolality, pH, purity ([redacted], SE-HPLC, [redacted], and [redacted]), DAR, water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, reconstitution time, potency (cell growth inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

### 2.2.5 Stability of drug product

Table 8 shows main stability studies for the drug product.

**Table 8. Summary of main stability studies for the drug product**

| | Number of batches | Storage condition | Study period | Container |
|---|---|---|---|---|
| Long-term | 3[*1] | 5 ± 3°C | 24 months[*3] | Amber glass vial with fluororesin laminated butyl rubber stopper |
| | 2[*2] | | 18 months[*4] | |
| Accelerated | 3[*1] | 25 ± 2°C/60 ± 5%RH | 6 months | |
| | 2[*2] | | | |
| Stress | 3[*1] | 40 ± 2°C/75 ± 5%RH | 6 months[*5] | |
| | 2[*2] | | | |
| Photostability | 1[*1] | Overall illumination of ≥1.2 million lux·h and integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |

*1, Formulation manufactured by Process 3 using the drug substance manufactured by Process [redacted] *2, formulation manufactured by the proposed manufacturing process using the drug substance manufactured either by Process [redacted] or Process [redacted]; *3, 1 batch of the formulation manufactured by Process 3 has been tested for [redacted] months, and the stability testing is ongoing up to [redacted] months; *4, 1 batch manufactured by the proposed manufacturing process has been tested for up to [redacted] months, and another batch for up to [redacted] months, and stability testing is ongoing up to [redacted] months; *5, 1 batch of the formulation manufactured by the proposed manufacturing process has been tested for [redacted] months

The long-term and accelerated tests showed no significant change in quality attributes throughout the testing period.

The results of stress testing included the following: an increasing trend of [redacted] in [redacted]; increasing trends of [redacted] and [redacted] in [redacted]; and an increasing trend of [redacted].

Photostability testing demonstrated that the drug product is photostable.

The applicant explained that the shelf life of the formulation manufactured by the proposed manufacturing process would be determined based on the findings including the test results at Month 24 for the 3 batches of the formulation manufactured by Process 3.

### 2.3 QbD

QbD approaches were used to develop MAAL-9001, MAAA-1162a, the drug substance, and the drug product. As shown in Table 9, quality control strategies for trastuzumab deruxtecan were established based on identification of CQAs and other evaluations. Quality attributes including product-related substances, product-related impurities [see Sections 2.1.1.5.2 and 2.1.3.3.2], process-related impurities [see Sections 2.1.1.5.3 and 2.1.3.3.3], and formulation attributes were identified based on the information obtained in the development stage of trastuzumab deruxtecan, relevant knowledge, and other factors.

**Table 9. List of identified CQAs**

| | |
|---|---|
| CQAs of MAAL-9001 | Appearance of solution/appearance, pH, identity, protein concentration, [redacted], bioburden, bacterial endotoxins, adventitious viruses, mycoplasma, molecular weight variants (high molecular weight species, monomers, low molecular weight species, fragments, and truncated fragments), [redacted], process-related impurities (HCPs, host cell DNA, [redacted] |
| CQAs of MAAA-1162a | Description (appearance), identification, optical rotation, related substances, content, [redacted] |
| CQAs of drug substance | Appearance, identity, osmolality, pH, [redacted], size variants, [redacted] impurities, [redacted], bacterial endotoxins, bioburden, protein concentration, [redacted], HCPs, host cell DNA, [redacted], adventitious viruses, mycoplasma, [redacted] |
| CQAs of drug product | Description (appearance), identification, osmolality, pH, reconstitution time, purity ([redacted], size variants, [redacted] impurities), [redacted], uniformity of dosage units, water content, bacterial endotoxins, sterility, foreign insoluble matter, insoluble particulate matter, protein concentration, [redacted] |

## 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 is adequately controlled. The drug product awaits further evaluation of data from the ongoing stability studies; therefore, the conclusion on the quality of the drug product will be discussed in Review Report (2).

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

In this section, unless otherwise specified, the trastuzumab deruxtecan formulations used were manufactured by Process A [see Section 2.1.3.2].

### 3.1 Primary pharmacodynamics

#### 3.1.1 Binding affinity to HER2 and other kinases (CTD 4.2.1.1-1)

The binding affinity of trastuzumab deruxtecan and MAAL-9001 for human HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4 (recombinant proteins) was evaluated by ELISA. Trastuzumab deruxtecan and MAAL-9001 bound to HER2, but did not bind to EGFR, HER3, or HER4.

The binding affinity of trastuzumab deruxtecan and MAAL-9001 for human, mouse, rat, and cynomolgus monkey HER2 (recombinant proteins) was evaluated by ELISA. Neither trastuzumab deruxtecan nor MAAL-9001 bound to mouse HER2 or rat HER2. Table 10 shows $K_d$ values of trastuzumab deruxtecan and MAAL-9001 for human HER2 and cynomolgus monkey HER2.

**Table 10. Binding affinity of trastuzumab deruxtecan and MAAL-9001 for HER2**

| Animal species | $K_d$ [95% CI] (ng/mL) | |
|---|---|---|
| | Trastuzumab deruxtecan | MAAL-9001 |
| Human | 7.33 [6.64, 8.08] | 7.84 [7.13, 8.62] |
| Cynomolgus monkey | 7.46 [6.72, 8.29] | 7.48 [6.77, 8.25] |

n = 3

#### 3.1.2 Induction of DNA damage and apoptosis (CTD 4.2.1.1-4)

The ability of trastuzumab deruxtecan and MAAA-1181a to induce DNA damage and apoptosis was evaluated using the human breast cancer KPL-4 cell line by measurement of phosphorylation of cell

cycle checkpoint kinase 1 (CHK1) and histone H2AX as indicators of DNA damage, and expression of truncated poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) as an indicator of apoptosis. The results showed that trastuzumab deruxtecan and MAAA-1181a induced DNA damage and apoptosis.

### 3.1.3 Inhibition of AKT phosphorylation (CTD 4.2.1.1-5)

The inhibitory effect of trastuzumab deruxtecan on phosphorylation of protein kinase B (AKT) was evaluated by ELISA using the human breast cancer SK-BR-3 cell line. The $EC_{50}$ [95% CI] for trastuzumab deruxtecan (n = 3) was 89.65 [55.29, 145.36] ng/mL.

### 3.1.4 ADCC activity (CTD 4.2.1.1-6, 4.2.1.1-7)

The ADCC activity of trastuzumab deruxtecan and MAAL-9001 against SK-BR-3 cell line was evaluated by chromium release assay using peripheral blood mononuclear cells (PBMCs) derived from 3 heathy adult donors as effector cells. Table 11 shows $EC_{50}$ values of trastuzumab deruxtecan and MAAL-9001.

**Table 11. ADCC activity of trastuzumab deruxtecan and MAAL-9001**

| | $EC_{50}$ [95% CI] (ng/mL) | |
|---|---|---|
| | Trastuzumab deruxtecan | MAAL-9001 |
| Subject 1 | — | — |
| Subject 2 | 3.83 [2.06, 7.13] | 2.12 [1.42, 3.17] |
| Subject 3 | 5.90 [3.78, 9.23] | 2.69 [1.63, 4.44] |

n = 3; "—", could not be calculated

### 3.1.5 Effects of growth inhibition on malignant tumor cell lines or tumor tissue samples

#### 3.1.5.1 *In vitro* (CTD 4.2.1.1-2)

The effects of growth inhibition of trastuzumab deruxtecan and MAAL-9001 on various human malignant tumor cell lines were examined with adenosine triphosphate (ATP) levels in living cells as an indicator. Table 12 shows $IC_{50}$ values of trastuzumab deruxtecan and MAAL-9001.

**Table 12. Effects of growth inhibition of trastuzumab deruxtecan and MAAL-9001 on various human malignant tumor cell lines**

| Cell line | Derived from | HER2 expression* | $IC_{50}$ value [95% CI] (ng/mL) | |
|---|---|---|---|---|
| | | | Trastuzumab deruxtecan | MAAL-9001 |
| Calu-3 | Lung cancer | Positive | 9.29 [6.81, 12.66] | >10,000 |
| NCI-N87 | Gastric cancer | | 25.36 [21.79, 29.53] | 204.20 [46.79, 891.25] |
| KPL-4 | Breast cancer | | 26.80 [23.82, 30.14] | >10,000 |
| SK-BR-3 | | | 6.65 [5.41, 8.17] | 65.92 [23.50, 184.96] |
| MDA-MB-468 | | Negative | >10,000 | >10,000 |

n = 3; *, evaluated by flow cytometry

### 3.1.5.2 *In vivo*

#### 3.1.5.2.1 Patient-derived breast cancer tissue samples or human breast cancer cell lines (CTD 4.2.1.1-11, 4.2.1.1-12, 4.2.1.1-13, 4.2.1.1-14)

The antitumor effects of trastuzumab deruxtecan,[7)] T-DM1, and MAAL-9002b[8)] were evaluated using patient-derived subcutaneous xenograft nude mouse models (n = 10/group) of (a) HER2-positive CTG-0708 breast cancer tissue samples,[9)] or (b) HER2 low-expressing CTG-2308 breast cancer tissue samples.[10)] Treatment was initiated on the following day when tumor volume reached 150 to 300 $mm^3$ (Day 0). On Day 0, a single intravenous dose of trastuzumab deruxtecan 3 or 10 mg/kg, T-DM1 10 mg/kg, or MAAL-9002b 10 mg/kg was administered, and tumor volume was calculated. On Day 21, statistically significant antitumor effects were observed in the trastuzumab deruxtecan groups and MAAL-9002b group compared with the vehicle[11)] control group (Figure 1).

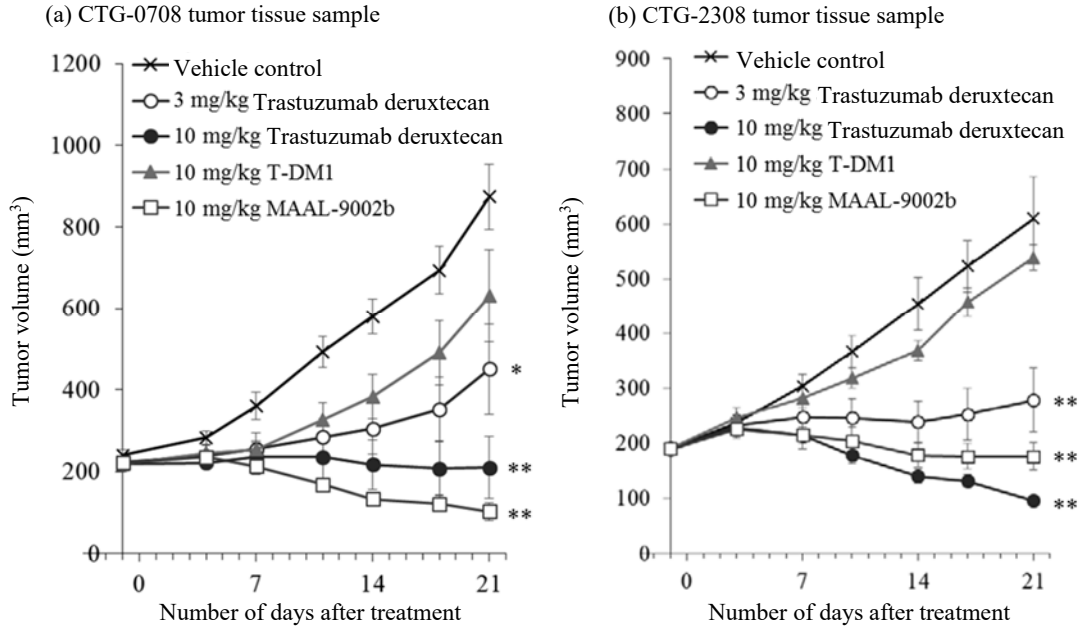



**Figure 1. Antitumor effects in subcutaneous xenograft nude mouse models of CTG-0708 or CTG-2308 tumor tissue samples**

n = 10; mean ± standard error; compared with the control group, *, $P < 0.05$, **, $P < 0.0001$ (Dunnett's test)

The antitumor effects of trastuzumab deruxtecan,[7)] T-DM1, and MAAL-9002b were evaluated using subcutaneous xenograft nude mouse models (n = 10/group) of HER2-expressing human breast cancer JIMT-1 cell line.[12)] A single intravenous dose of trastuzumab deruxtecan 3 or 10 mg/kg, T-DM1 10 mg/kg, or MAAL-9002b 10 mg/kg was administered 10 days after tumor xenograft (Day 0), and tumor volume was calculated. On Day 21, statistically significant antitumor effects were observed in the

7) Trastuzumab deruxtecan manufactured by Process B [see Section 2.1.3.2].
8) ADC composed of MAAL-9001, MAAA-1181a, and a peptide-linker, similarly to trastuzumab deruxtecan, but has a DAR of 3.7.
9) Tumor tissue (3 specimens) was collected from nude mice xenografted with CTG-0708 tumor samples, and evaluated by immunohistochemistry (IHC). All specimens had an IHC score of 3+.
10) Tumor tissue (3 specimens) was collected from nude mice xenografted with CTG-2308 tumor samples, and evaluated by IHC. Two of the specimens had an IHC score of 0, while the other specimen had an IHC score of 2+.
11) 25 mmol/L histidine and a buffer containing 9% sucrose (pH5.5).
12) HER2 expression was evaluated by flow cytometry (e.g., *Cancer Cell.* 2016;29:117-29).

trastuzumab deruxtecan groups, T-DM1 group, and MAAL-9002b group compared with the vehicle[11] control group ($P < 0.0001$ for all groups; Dunnett's test).

#### 3.1.5.2.2 Patient-derived gastric cancer tissue samples or human gastric cancer cell lines (CTD 4.2.1.1-13, 4.2.1.1-15, 4.2.1.1-16)

Using subcutaneous xenograft nude mouse models (n = 8/group) of HER2-expressing gastric cancer NIBIO G016 tumor tissue samples,[13] the antitumor effects of trastuzumab deruxtecan,[7] T-DM1, and MAAL-9002b were evaluated. A single intravenous dose of trastuzumab deruxtecan 3 or 10 mg/kg, T-DM1 10 mg/kg, or MAAL-9002b 10 mg/kg was administered 34 days after tumor xenograft (Day 0), and tumor volume was calculated. On Day 21, statistically significant antitumor effects were observed in the trastuzumab deruxtecan 3 and 10 mg/kg groups, and MAAL-9002b 10 mg/kg group compared with the vehicle[11] control group ($P < 0.0001$ for all groups; Dunnett's test).

The antitumor effects of trastuzumab deruxtecan[7] and T-DM1 were evaluated using subcutaneous xenograft nude mouse models (n = 8/group) of (a) HER2-expressing NCI-N87 cell line,[14] (b) HER2 non-expressing human gastric cancer MKN45 cell line,[15] or (c) a mixture of NCI-N87 and MKN45 cell lines. Treatment was initiated on the day when tumor volume reached 150 to 250 $mm^3$ (Day 0). On Day 0, a single intravenous dose of trastuzumab deruxtecan or T-DM1 10 mg/kg was administered, and tumor volume was calculated. On Day 14, compared with the vehicle[11] control group, statistically significant antitumor effects were observed in (a) the trastuzumab deruxtecan and T-DM1 groups in the evaluation of the subcutaneous xenograft mouse models of the NCI-N87 cell line only, and (c) the trastuzumab deruxtecan group in the evaluation of the subcutaneous xenograft mouse models of the NCI-N87 and MKN45 cell line mixture ($P < 0.0001$ for all groups; Dunnett's test).

The applicant explained that the above evaluation results of (c) suggest that after internalization into HER2-expressing tumor cells, trastuzumab deruxtecan released MAAA-1181a, which may have also acted on HER2 non-expressing tumor cells, resulting in an antitumor effect.

## 3.2 Safety pharmacology

### 3.2.1 Effects on hERG potassium current (CTD 4.2.1.3-1)

Using CHO cell lines transfected with human ether-a-go-go-related gene (hERG), the effects of MAAA-1181a 1, 3, and 10 μmol/L on hERG potassium current were evaluated. The percentage inhibition of hERG potassium current was −4.24 ± 2.59%, 0.42 ± 2.95%, and −0.74 ± 4.18% at 1, 3, and 10 μmol/L, respectively (mean ± standard deviation; n = 5).

---

13) HER2 expression was evaluated by IHC and fluorescence *in situ* hybridization (*Clin Cancer Res.* 2016;22:5097-108).
14) Tumor tissue (3 specimens) was collected from nude mice xenografted with NCI-N87 cells, and evaluated by IHC. All specimens had an IHC score of 3+.
15) Tumor tissue (3 specimens) was collected from nude mice xenografted with MKN45 cells, and evaluated by IHC. All specimens had an IHC score of 0.

### 3.2.2 Effects on the central nervous system, cardiovascular system, and respiratory system (CTD 4.2.1.3-2)

A single intravenous dose of trastuzumab deruxtecan 30 or 78.8 mg/kg was administered to cynomolgus monkeys (n = 4) to investigate the effects of trastuzumab deruxtecan on blood pressure, heart rate, electrocardiography, respiratory rate, blood gas, body temperature, neurobehavioral function, clinical signs, and other factors. Findings that included vomiting were observed at trastuzumab deruxtecan 78.8 mg/kg.

The applicant explained that cautionary advice regarding vomiting will be given to healthcare professionals in an appropriate manner using the package insert because vomiting has also been reported in clinical studies [see Section 7.R.3.1].

## 3.R Outline of the review conducted by PMDA

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

### 3.R.1 Mechanism of action and efficacy of trastuzumab deruxtecan

The applicant's explanation about the mechanism of action of trastuzumab deruxtecan and its efficacy in HER2-positive breast cancer:

Trastuzumab deruxtecan is an ADC formed by conjugation of the anti-HER2 humanized monoclonal antibody of IgG1 subclass (MAAL-9001) with the topoisomerase I inhibitor derivative of exatecan (MAAA-1181a) through a peptide linker. Trastuzumab deruxtecan binds to HER2 expressed on the tumor cell membrane [see Section 3.1.1]. Upon internalization into the cell, the linker undergoes hydrolysis, releasing MAAA-1181a (drug payload). The released payload is thought to induce DNA damage, apoptosis and other effects [see Section 3.1.2], leading to inhibition of tumor growth.

In addition to the mechanism of action described above, findings including the following suggest that the efficacy of trastuzumab deruxtecan can be expected in the treatment of HER2-positive breast cancer.

- In the study using subcutaneous xenograft nude mouse models of the HER2-expressing human breast cancer cell line or patient-derived breast cancer tissue samples, trastuzumab deruxtecan showed antitumor effects [see Section 3.1.5.2.1].
- In a study using subcutaneous xenograft nude mouse models of the T-DM1-resistant[16)] NCI-N87 cell line, trastuzumab deruxtecan has been reported to show antitumor effects (*Int J Cancer*. 2017;141:1682-9).

The applicant's explanation about the differences in pharmacological characteristics between trastuzumab deruxtecan and T-DM1, an ADC that has been approved in Japan for the treatment of HER2-positive breast cancer:

16) T-DM1 was added to NCI-N87 cells by gradually increasing doses up to 4 μg/mL to prepare T-DM1-resistant NCI-N87 cells in which T-DM1 was not shown to have an antitumor effect.

Both trastuzumab deruxtecan and T-DM1 bind to HER2 expressed on the tumor cell membrane, and following internalization into the cell, their released payloads induce cell damage.

In contrast to the above, there are differences between trastuzumab deruxtecan and T-DM1 including the following: (a) compared with T-DM1, trastuzumab deruxtecan has a higher DAR (*Pharmacol Ther*. 2018;181:126-42); (b) the payload of trastuzumab deruxtecan has a higher cell membrane permeability compared with that of T-DM1 (*Cancer Sci.* 2016;107:1039-46). Unlike T-DM1, these differences may have been responsible for the antitumor effects of trastuzumab deruxtecan observed in the studies including the following: the study using subcutaneous xenograft nude mouse models of HER2 low-expressing patient-derived breast cancer tissue samples [see Section 3.1.5.2.1]; the study using subcutaneous xenograft nude mouse models of a mixture of HER2 non-expressing and HER2-expressing human malignant tumor cell lines [see Section 3.1.5.2.2].

PMDA accepted the applicant's explanation.

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

In this section, unless otherwise specified, the trastuzumab deruxtecan formulations used were manufactured by Process A [see Section 2.1.3.2]. The pharmacokinetics (PK) of trastuzumab deruxtecan in animals was studied in rats, monkeys and other animals. Human or animal biological samples were used to evaluate plasma protein binding, drug metabolizing enzymes, transporters, and other factors of trastuzumab deruxtecan and its component, MAAA-1181a.

In this section, the following notation is used: "MAAL-9001" is trastuzumab, an anti-HER2 antibody, which is the intermediate of trastuzumab deruxtecan; "total MAAL-9001" is the sum of trastuzumab conjugated and unconjugated with the payload (MAAA-1181a); "MAAA-1181a" is the drug payload (exatecan derivative) released from trastuzumab deruxtecan; and MAAA-1181a that is not linked to the antibody portion (MAAL-9001) is referred to as "unconjugated MAAA-1181a."

### 4.1 Analytical methods

#### 4.1.1 Assay methods for trastuzumab deruxtecan

Trastuzumab deruxtecan in rat and monkey plasma was determined by ligand binding assay using solid phased [redacted], [redacted]-labeled [redacted], and [redacted]-labeled [redacted].

#### 4.1.2 Assay methods for total MAAL-9001

Total MAAL-9001 in rat and monkey plasma was determined by ligand binding assay using solid phased [redacted], [redacted]-labeled [redacted], and [redacted]-labeled [redacted].

### 4.1.3 Assay of unconjugated MAAA-1181a

The unconjugated MAAA-1181a in rat and monkey plasma was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS).

### 4.1.4 Assay of anti-trastuzumab deruxtecan antibodies

Anti-trastuzumab deruxtecan antibodies (anti-drug antibodies against trastuzumab deruxtecan, ADAs) in rat and monkey plasma were measured by a bridging electrochemiluminescence (ECL) assay using solid phased [redacted]-labeled trastuzumab deruxtecan, and [redacted]-labeled trastuzumab deruxtecan.

## 4.2 Absorption

### 4.2.1 Single-dose study

A single intravenous dose of trastuzumab deruxtecan 0.1, 0.3, 1, or 3 mg/kg was administered to male monkeys to investigate plasma trastuzumab deruxtecan concentrations and other parameters (Table 13). $AUC_{inf}$ increased in a greater than dose-proportional manner for trastuzumab deruxtecan and total MAAL-9001 within the dose range studied. The applicant explained that this increase might be due to saturation of antigen-dependent elimination of trastuzumab deruxtecan and MAAL-9001 through HER2 binding with increasing dose. Overall, MAAA-1181a was below the lower limits of quantitation at all timepoints.

No ADAs were detected in any animal following administration of trastuzumab deruxtecan.

**Table 13. Pharmacokinetic parameters of trastuzumab deruxtecan and total MAAL-9001 (male monkeys; single intravenous dose administration)**

| Analyte | Dose (mg/kg) | $AUC_{inf}$ (μg·day/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 0.1 | 1.87 ± 0.487 | 0.641 ± 0.137 | 55.7 ± 13.4 | 45.3 ± 6.73 |
| | 0.3 | 8.43 ± 0.859 | 0.686 ± 0.191 | 35.9 ± 3.78 | 30.6 ± 3.89 |
| | 1 | 46.1 ± 4.52 | 2.90 ± 0.0829 | 21.8 ± 2.27 | 55.4 ± 2.61 |
| | 3 | 216 ± 20.7 | 3.92 ± 1.71 | 14.0 ± 1.35 | 52.7 ± 11.3 |
| Total MAAL-9001 | 0.1 | 2.00 ± 0.632 | 0.648 ± 0.159 | 53.2 ± 15.2 | 43.1 ± 6.21 |
| | 0.3 | 7.67 ± 0.382 | 0.706 ± 0.217 | 39.2 ± 2.01 | 34.4 ± 7.51 |
| | 1 | 43.4 ± 9.11 | 4.54 ± 0.929 | 23.8 ± 5.43 | 72.4 ± 6.78 |
| | 3 | 211 ± 27.5 | 4.60 ± 1.54 | 14.4 ± 1.82 | 61.4 ± 18.2 |

Mean ± standard deviation; n = 3

### 4.2.2 Repeated-dose studies

Intravenous doses of trastuzumab deruxtecan 20, 60, or 197 mg/kg were administered to male and female rats Q3W for 6 weeks to investigate plasma trastuzumab deruxtecan concentrations and other parameters (Table 14). The $C_{max}$ and $AUC_{21day}$ generally increased in a dose-proportional manner for trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a within the dose range studied, and no clear differences were noted between the sexes. No clear effects of repeated dosing of trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a on their PK parameters were observed.

No ADAs were detected in any animal following administration of trastuzumab deruxtecan.

**Table 14. Pharmacokinetic parameters of trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a (male and female rats; 6-week repeated intravenous dose administration)**

| Analyte | Dose (mg/kg) | Day measured | $C_{max}$ (μg/mL*1) | | $AUC_{21day}$ (μg·day/mL*2) | | $t_{1/2}$ (day) | |
|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Male | Female | Male | Female |
| Trastuzumab deruxtecan | 20 | 1 | 439 ± 41.6 | 497 ± 37.7 | 1,776 ± 64 | 1,869 ± 188 | 8.07 ± 0.0631 | 7.61 ± 0.270 |
| | | 22 | 613 ± 28.3 | 615 ± 31.7 | 2,676 ± 226 | 2,339 ± 265 | 8.47 ± 0.481 | 7.63 ± 0.660 |
| | 60 | 1 | 1,400 ± 47.7 | 1,510 ± 174 | 4,903 ± 493 | 4,871 ± 542 | 8.52 ± 0.827 | 8.67 ± 1.17 |
| | | 22 | 1,740 ± 75.5 | 1,890 ± 130 | 6,756 ± 415 | 7,391 ± 536 | 8.98 ± 1.61 | 9.56 ± 0.731 |
| | 197 | 1 | 4,300 ± 348 | 5,070 ± 444 | 13,824 ± 1,420 | 15,096 ± 2,432 | 5.78 ± 2.66 | 6.88 ± 2.54 |
| | | 22 | 6,410 ± 121 | 5,730 ± 558 | 14,264 ± 4,063 | 19,818 ± 2,159 | 5.20 ± 2.44 | 8.43 ± 1.14 |
| Total MAAL-9001 | 20 | 1 | 459 ± 48.5 | 514 ± 22.9 | 2,095 ± 106 | 2,182 ± 156 | 9.79 ± 0.390 | 9.76 ± 0.735 |
| | | 22 | 611 ± 41.4 | 632 ± 12.7 | 3,035 ± 200 | 2,736 ± 358 | 11.0 ± 0.376 | 9.04 ± 1.01 |
| | 60 | 1 | 1,530 ± 77.6 | 1,470 ± 65.1 | 6,017 ± 579 | 6,067 ± 231 | 10.4 ± 0.337 | 10.4 ± 1.16 |
| | | 22 | 2,030 ± 191 | 1,780 ± 86.5 | 8,069 ± 545 | 8,448 ± 461 | 9.64 ± 1.72 | 11.7 ± 1.29 |
| | 197 | 1 | 4,980 ± 262 | 4,700 ± 533 | 17,481 ± 2,054 | 17,036 ± 2,396 | 6.12 ± 2.85 | 7.86 ± 3.12 |
| | | 22 | 6,560 ± 475 | 5,970 ± 736 | 17,895 ± 5,189 | 22,533 ± 2,460 | 5.13 ± 2.41 | 10.3 ± 2.04 |
| MAAA-1181a | 20 | 1 | 0.819 ± 0.108 | 1.21 ± 0.370 | 2.88 ± 0.287 | 2.45 ± 0.657 | 4.24 ± 0.506 | 3.16 ± 0.641 |
| | | 22 | 1.41 ± 0.284 | 1.19 ± 0.362 | 4.68 ± 0.733 | 3.02 ± 0.515 | 6.64 ± 0.524 | 5.73 ± 1.95 |
| | 60 | 1 | 2.49 ± 0.351 | 3.54 ± 1.21 | 8.57 ± 0.456 | 6.86 ± 0.690 | 3.90 ± 1.30 | 3.46 ± 0.703 |
| | | 22 | 4.20 ± 0.287 | 4.36 ± 0.397 | 14.4 ± 0.606 | 10.0 ± 1.24 | 6.14 ± 0.373 | 6.90 ± 1.12 |
| | 197 | 1 | 9.89 ± 1.34 | 15.0 ± 3.57 | 31.9 ± 3.42 | 28.1 ± 3.17 | 3.57 ± 1.24 | 5.34 ± 0.430 |
| | | 22 | 13.4 ± 1.06 | 14.0 ± 4.25 | 40.3 ± 9.87 | 32.4 ± 3.09 | 3.23 ± 1.56 | 6.37 ± 1.30 |

Mean ± standard deviation; n = 4; *1, values for MAAA-1181a are expressed in ng/mL; *2, values for MAAA-1181a are expressed in ng·day/mL

Trastuzumab deruxtecan[17] 3, 10, or 30 mg/kg was administered intravenously Q3W to male and female monkeys for 3 months to investigate plasma trastuzumab deruxtecan concentrations and other parameters (Table 15). $C_{max}$ and $AUC_{21day}$ generally increased in a dose-proportional manner for trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a within the dose range studied, and no clear differences were noted between the sexes. No clear effects of repeated dosing of trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a on their PK parameters were observed.

No ADAs were detected in any animal following administration of trastuzumab deruxtecan.

17) Trastuzumab deruxtecan manufactured by Process B [see Section 2.1.3.2].

**Table 15. Pharmacokinetic parameters of trastuzumab deruxtecan, total MAAL-9001, and MAAA-1181a (male and female monkeys; 3-month repeated intravenous dose administration)**

| Analyte | Dose (mg/kg) | n | Day measured | $C_{max}$ (μg/mL*1) | | $AUC_{21day}$ (μg·day/mL*2) | | $t_{1/2}$ (day) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Male | Female | Male | Female | Male | Female |
| Trastuzumab deruxtecan | 3 | 4 | 1 | 101 ± 9.08 | 95.3 ± 8.18 | 317 ± 26.9 | 268 ± 31.3 | 3.95 ± 0.227 | 3.85 ± 0.183 |
| | | | 64 | 78.2 ± 15.0 | 98.4 ± 7.97 | 286 ± 45.3 | 285 ± 29.1 | 4.32 ± 0.579 | 3.84 ± 0.383 |
| | 10 | 4 | 1 | 295 ± 33.9 | 339 ± 31.8 | 1,220 ± 113 | 1,080 ± 125 | 5.56 ± 0.457 | 5.13 ± 0.385 |
| | | | 64 | 320 ± 79.0 | 352 ± 67.8 | 1,390 ± 170 | 1,110 ± 226 | 6.08 ± 0.521 | 5.05 ± 1.07 |
| | 30 | 6 | 1 | 877 ± 88.5 | 899 ± 58.9 | 4,090 ± 685 | 3,770 ± 462 | 7.71 ± 0.666 | 6.53 ± 0.524 |
| | | | 64 | 898 ± 130 | 1,090 ± 202 | 5,030 ± 771 | 4,910 ± 802 | 9.02 ± 1.42 | 7.40 ± 0.878 |
| Total MAAL-9001 | 3 | 4 | 1 | 113 ± 12.0 | 96.9 ± 4.83 | 357 ± 31.8 | 287 ± 36.8 | 4.33 ± 0.340 | 4.09 ± 0.304 |
| | | | 64 | 78.4 ± 12.1 | 106 ± 11.3 | 297 ± 54.8 | 319 ± 41.0 | 4.73 ± 0.569 | 4.18 ± 0.491 |
| | 10 | 4 | 1 | 280 ± 41.3 | 312 ± 58.2 | 1,280 ± 118 | 1,130 ± 141 | 6.25 ± 0.473 | 5.89 ± 0.587 |
| | | | 64 | 295 ± 59.3 | 320 ± 60.8 | 1,450 ± 208 | 1,150 ± 260 | 7.04 ± 0.649 | 5.80 ± 1.22 |
| | 30 | 6 | 1 | 845 ± 112 | 886 ± 92.1 | 4,300 ± 731 | 3,790 ± 445 | 9.25 ± 1.23 | 7.95 ± 1.18 |
| | | | 64 | 949 ± 122 | 1,090 ± 190 | 5,960 ± 1,100 | 5,500 ± 1,040 | 9.56 ± 1.28 | 8.31 ± 1.25 |
| MAAA-1181a | 3 | 4 | 1 | 0.242 ± 0.0236 | 0.248 ± 0.106 | 0.779 ± 0.122 | 0.874 ± 0.507 | — | — |
| | | | 64 | 0.223 ± 0.0708 | 0.186 ± 0.0277 | 0.634 ± 0.215 | 0.294 ± 0.0532 | — | — |
| | 10 | 4 | 1 | 0.656 ± 0.0912 | 1.02 ± 0.451 | 2.52 ± 0.876 | 2.75 ± 1.40 | 3.33 ± 1.11 | 2.35 ± 0.487 |
| | | | 64 | 0.842 ± 0.207 | 1.28 ± 0.659 | 3.06 ± 0.289 | 2.39 ± 1.05 | 3.61 ± 0.545 | 2.36 ± 0.963 |
| | 30 | 6 | 1 | 2.71 ± 0.546 | 3.90 ± 1.11 | 9.91 ± 2.68 | 12.0 ± 3.52 | 7.15 ± 1.85 | 4.07 ± 1.42 |
| | | | 64 | 2.33 ± 0.450 | 4.86 ± 1.88 | 11.0 ± 2.42 | 13.5 ± 4.43 | 6.15 ± 1.78 | 3.72 ± 1.49 |

Mean ± standard deviation; "—", not calculated; *1, values for MAAA-1181a are expressed in ng/mL; *2, values for MAAA-1181a are expressed in ng·day/mL

## 4.3 Distribution

### 4.3.1 Tissue distribution

A single intravenous dose of trastuzumab deruxtecan 6.4 mg/kg containing $^{3}$H-labeled MAAL-9001 was administered to male monkeys to investigate tissue distribution of radioactivity by quantitative whole body autoradioluminography. Radioactivity was widely distributed across the tissues. One day following administration (Day 1), the tissue-to-blood radioactivity concentration ratio was particularly high in the kidney (0.95), lung (0.91), liver (0.72), adrenal gland (0.61), epididymis (0.54), prostate (0.51), and spleen (0.51). Radioactivity concentrations in tissue decreased as those in blood decreased. The results did not indicate any trend towards persistence of radioactivity in tissue.

A single intravenous dose of trastuzumab deruxtecan 6.4 mg/kg containing $^{14}$C-labeled MAAA-1181a was administered to male monkeys to investigate tissue distribution of radioactivity by quantitative whole body autoradioluminography. Radioactivity was widely distributed across the tissues. On Day 1, the tissue-to-blood radioactivity concentration ratio was particularly high in large intestine content (2.48), the lung (0.71), kidney (0.44), adrenal gland (0.43), liver (0.42), spleen (0.39), and small intestine content (0.32). Radioactivity concentrations in tissue decreased as those in blood decreased. The results did not indicate any trend towards persistence of radioactivity in tissue.

### 4.3.2 Plasma protein binding

After incubating MAAA-1181a (10, 30, and 100 ng/mL) in plasma from mice, rats, monkeys, or humans at 37°C for 5 minutes, protein binding of MAAA-1181a was investigated by ultracentrifugation. The

plasma protein binding ratio of MAAA-1181a was roughly constant across the species independent of concentration: 90.3% to 92.5% (mouse), 94.2% to 96.7% (rat), 86.5% to 89.1% (monkey), and 96.8% to 98.0% (human).

#### 4.3.3 Distribution in blood cells

Blood from mice, rats, monkeys, or humans was incubated with $^{14}$C-labeled MAAA-1181a (10, 30, and 100 ng/mL) at 37°C for 10 minutes, and distribution of radioactivity in blood cells was investigated. The distribution of radioactivity in blood cells was roughly constant across the species independent of concentration with the blood-to-plasma radioactivity concentration ratio being 0.82 to 0.85 (mouse), 0.81 to 0.87 (rat), 0.92 to 0.95 (monkey), and 0.59 to 0.62 (human). The applicant explained that the results indicated that MAAA-1181a is distributed primarily in plasma in all the species studied.

#### 4.3.4 Placental transfer and fetal transfer

Neither placental transfer nor fetal transfer of trastuzumab deruxtecan have been studied. The applicant explained that trastuzumab, which has an amino acid sequence identical to that of MAAL-9001, the antibody component of trastuzumab deruxtecan, has been reported to cross the placenta to the fetus; therefore, trastuzumab deruxtecan may also cross the placenta to the fetus (see Review Reports including Herceptin for Intravenous Infusion 150, dated March 8, 2001).

### 4.4 Metabolism

#### 4.4.1 Stability in plasma

The stability of trastuzumab deruxtecan (10 and 100 μg/mL) in plasma was studied by incubating with mouse, rat, monkey, or human plasma, or a phosphate-buffered saline containing 1% bovine serum albumin (BSA) at 37°C for 21 days. The release rate of MAAA-1181a in plasma and buffer at trastuzumab deruxtecan 10 and 100 μg/mL was as follows: 1.2% and 1.2% (in mouse plasma at 10 and 100 μg/mL, respectively; the same applies hereinafter); 1.8% and 1.7% (rat); 3.9% and 3.5% (monkey); 2.1% and 1.5% (human); and 0.3% and 0.4% (buffer). The applicant explained that the results showed a limited level of release of MAAA-1181a from trastuzumab deruxtecan into plasma, suggesting the stability of trastuzumab deruxtecan in plasma.

#### 4.4.2 *In vitro*

Trastuzumab deruxtecan 0.49 mg/mL manufactured by Process A [see Section 2.1.3.2] was incubated with hepatocytes from rats, monkeys, or humans at 37°C for 6 hours to evaluate metabolites. In hepatocytes across the animal species and human, MAAA-1181a, MAAA-1430a (a methyl glycine amide of MAAA-1181a), MAAA-1431a and MAAA-1458a (both are cysteine conjugates of the linker), MAAA-1438a (a succinimide of the linker), and MAAA-1437a (thiomethylated linker) were commonly detected.

The applicant explained that the results below suggest cytochrome P450 (CYP)3A is mainly involved in the oxidative metabolism of MAAA-1181a. The pharmacokinetic drug interactions of trastuzumab

deruxtecan with CYP3A inhibitors and organic anion transporting polypeptide (OATP)1B inhibitors will be discussed in Section "6.2.3.1 Drug interactions with itraconazole or ritonavir."

- A recombinant human CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5) was incubated with MAAA-1181a (10 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 30 minutes to determine CYP isoforms involved in the metabolism of MAAA-1181a. In the presence of CYP1A2, CYP2D6, CYP3A4, or CYP3A5, MAAA-1468a (an oxide of MAAA-1181a) was detected.
- In the presence of NADPH and the inhibitor of each CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A),[18)] human liver microsomes were incubated with MAAA-1181a (10 μmol/L) at 37°C for 30 minutes to determine CYP isoforms involved in the metabolism of MAAA-1181a. In the presence of the inhibitor of CYP3A, the metabolism of MAAA-1181a was inhibited by 94.9%. In the presence of other CYP inhibitors studied, no clear inhibition of the metabolism of MAAA-1181a was observed with the maximum inhibition being 16.3%.

#### 4.4.3 *In vivo*

A single intravenous dose of trastuzumab deruxtecan 6.4 mg/kg containing $^{14}$C-labeled MAAA-1181a was administered to male monkeys to evaluate metabolites in plasma, urine, and feces, and the following results were obtained:

- Radioactivity equivalent to low molecular weight metabolites of trastuzumab deruxtecan was detected in plasma collected up to 312 hours post-dose, and its concentration accounted for <1.1% of the total radioactivity in plasma.
- Mainly MAAA-1181a was detected as a metabolite in urine and feces up to 144 hours post-dose.

A single intravenous dose of $^{14}$C-labeled MAAA-1181a 1 mg/kg was administered to bile-duct cannulated and non-cannulated male rats to evaluate metabolites in urine, feces, and bile, and the following results were obtained:

- In non-cannulated rats, mainly unchanged MAAA-1181a was detected in urine and feces collected up to 48 hours post-dose, accounting for 23.4% (urine) and 61.1% (feces) of the total radioactivity administered.
- In bile-duct cannulated rats, mainly unchanged MAAA-1181a was detected in bile collected up to 48 hours post-dose, accounting for 63.7% of the total radioactivity administered.

### 4.5 Excretion

#### 4.5.1 Urinary, fecal, expiratory, and biliary excretion

The applicant's explanation:

The evaluation results below suggest that trastuzumab deruxtecan and its metabolites are mainly excreted in feces, while MAAA-1181a and its metabolites are mainly excreted in feces via the bile.

---

[18)] The following compounds were used as inhibitors for the CYP isoforms: furafylline (CYP1A2), thiotepa (CYP2B6), montelukast (CYP2C8), sulfaphenazole (CYP2C9), S-*N*-3-benzylnirvanol (CYP2C19), quinidine anhydrous (CYP2D6), and ketoconazole (CYP3A).

- Following single dose intravenous administration of trastuzumab deruxtecan 6.4 mg/kg containing $^{14}$C-labeled MAAA-1181a to male monkeys, 18.7% (urine) and 67.3% (feces) of the total radioactivity administered was detected up to 14 days post-dose.
- Following single dose intravenous administration of $^{14}$C-labeled MAAA-1181a 1 mg/kg to male rats, 27.2% (urine), 70.4% (feces), and 0.1% (expiratory) of the total radioactivity administered was detected up to 7 days post-dose.
- Following single dose intravenous administration of $^{14}$C-labeled MAAA-1181a 1 mg/kg to bile-duct cannulated male rats, 21.9% (urine), 2.7% (feces), and 71.6% (bile) of the total radioactivity administered was detected up to 2 days post-dose.

#### 4.5.2 Excretion in breast milk

Excretion of trastuzumab deruxtecan in breast milk have not been studied. The applicant explained that trastuzumab, which has an amino acid sequence identical to that of MAAL-9001, the antibody component of trastuzumab deruxtecan, has been reported to be excreted in breast milk; therefore, trastuzumab deruxtecan may also be excreted in breast milk (see Review Reports including Herceptin for Intravenous Infusion 150, dated March 8, 2001).

### 4.6 Pharmacokinetic drug interactions

#### 4.6.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic drug interactions via the inhibition of metabolizing enzymes by MAAA-1181a:

On the basis of the $C_{max}$ (16.7 nmol/L[19)]) for MAAA-1181a at the proposed dosage and administration of trastuzumab deruxtecan and the evaluation results shown below, it is unlikely that pharmacokinetic drug interactions will occur via the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A by MAAA-1181a when trastuzumab deruxtecan is used clinically.

- In the presence of NADPH, human liver microsomes were pre-incubated with MAAA-1181a (0.05-50 μmol/L) for 0 or 30 minutes, followed by incubation with substrates[20)] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A to investigate reversible inhibition and time-dependent inhibition of CYP isoforms by MAAA-1181a. MAAA-1181a did not show a clear reversible inhibitory effect or time-dependent inhibitory effect on the metabolism of the CYP substrates.

#### 4.6.2 Enzyme induction

The applicant's explanation about the pharmacokinetic drug interactions via the induction of metabolizing enzymes by MAAA-1181a:

---

19) The $C_{max}$ value following the first dose of trastuzumab deruxtecan 5.4 mg/kg, which was administered intravenously Q3W in the global phase I study (Study J101, Parts 1 and 2).

20) The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), bupropion (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), and R-bufuralol (CYP2D6); testosterone and midazolam as substrates for CYP3A.

On the basis of the $C_{max}$ (16.7 nmol/L[19)]) for MAAA-1181a at the proposed dosage and administration of trastuzumab deruxtecan and the evaluation results shown below, it is unlikely that pharmacokinetic drug interactions will occur via the induction of CYP1A2, CYP2B6, and CYP3A4 by MAAA-1181a when trastuzumab deruxtecan is used clinically.

- In the presence of MAAA-1181a (0.03-30 μmol/L), human hepatocytes were incubated for 72 hours, and messenger ribonucleic acid (mRNA) expression and enzyme activity of CYP1A2, CYP2B6 and CYP3A4 were evaluated. In the positive controls,[21)] the mRNA expression levels increased by a maximum of 13.8-fold (CYP1A2), 4.1-fold (CYP2B6), and 65.2-fold (CYP3A4) compared with that of the vehicle (0.1% dimethyl sulfoxide [DMSO]), and the enzyme activity increased by a maximum of 8.2-fold (CYP1A2), 13.5-fold (CYP2B6), and 17.0-fold (CYP3A4) compared with that of the vehicle (0.1% DMSO). In contrast, MAAA-1181a showed no clear inductive effect on the mRNA expression levels or enzyme activity of any of the CYP isoforms studied.

### 4.6.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic drug interactions of MAAA-1181a:

The findings, including the study results shown below, suggest that MAAA-1181a is not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion (MATE)1, bile salt export pump (BSEP), multidrug resistance associated protein (MRP)2, or MRP3, but is a substrate of OATP1B1, OATP1B3, MATE2-K, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and MRP1. However, given that (a) there was no particular safety concern when trastuzumab deruxtecan was coadministered with the inhibitor of P-gp, BCRP, or other transporters in the global phase I study (Study A104); and (b) renal excretion is not a significant route of elimination of MAAA-1181a [see Section 4.5.1], it is unlikely that pharmacokinetic drug interactions will pose a problem when trastuzumab deruxtecan is clinically coadministered with a MATE2-K, P-gp, BCRP, or MRP1 inhibitor. The pharmacokinetic drug interactions of trastuzumab deruxtecan with OATP1B inhibitors will be discussed in Section "6.2.3.1 Drug interactions with itraconazole or ritonavir."

- Using the human embryonic kidney (HEK)293 cell line expressing human OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, a mouse renal segment $S_2$-derived cell line expressing human OAT1 or OAT3, membrane vesicles expressing human BSEP, and the Caco-2 cell line, transport of $^{14}$C-labeled MAAA-1181a (0.03-10 μmol/L[22)]) mediated by the above transporters was investigated. The $^{14}$C-labeled MAAA-1181a uptake ratio of transporter-expressing cells to transporter non-expressing cells was 54.9 for OATP1B1, 5.0 for OATP1B3, and 3.8 for MATE2-K. The ratio of the apparent permeability coefficient value in basolateral to apical direction ($P_{app\ B\rightarrow A}$) to that in apical to basolateral direction ($P_{app\ A\rightarrow B}$) was 10.7 in the absence of P-gp and

21) The following compounds were used as the positive controls for the CYP isoforms: omeprazole 0.3 to 50 μmol/L (CYP1A2), phenobarbital 0.01 to 3 μmol/L (CYP2B6), and rifampicin 0.1 to 30 μmol/L (CYP3A4).

22) The assays were performed at the following concentrations: at 1 μmol/L for OAT1, OAT3, OCT1, OCT2, MATE1, BSEP, P-gp and BCRP; and at 0.03 to 10 μmol/L for OATP1B1, OATP1B3, and MATE2-K.

BCRP inhibitors, 4.37 in the presence of P-gp inhibitor (verapamil, 100 μmol/L), 4.44 in the presence of BCRP inhibitor (novobiocin, 10 μmol/L), and 4.43 in the presence of the dual P-gp/BCRP inhibitor (GF120918, 10 μmol/L). On the other hand, no transport of $^{14}$C-labeled MAAA-1181a mediated by OAT1, OAT3, OCT1, OCT2, MATE1, or BSEP was observed.

- Using membrane vesicles prepared from the Sf9 insect cell line expressing human MRP1, MRP2, or MRP3, or from the HEK293 cell line, transport of $^{14}$C-labeled MAAA-1181a (2 or 20 μmol/L) mediated by the above transporters was investigated. The results indicated an ATP-dependent transport of $^{14}$C-labeled MAAA-1181a in the MRP1-expressing membrane vesicles, and this transport was inhibited by the MRP1 inhibitor (benzbromarone, 150 μmol/L). In contrast, no ATP-dependent transport of $^{14}$C-labeled MAAA-1181a mediated by MRP2 or MRP3 was detected.

On the basis of the $C_{max}$ (16.7 nmol/L[19)]) for MAAA-1181a at the proposed dosage and administration of trastuzumab deruxtecan and the evaluation results shown below, it is unlikely that pharmacokinetic drug interactions will occur via the inhibition of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and BSEP by MAAA-1181a when trastuzumab deruxtecan is used clinically.

- Using the HEK293 cell line expressing human OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, an $S_2$ cell line expressing human OAT1 or OAT3, membrane vesicles expressing human BSEP, and the Caco-2 cell line, inhibition of transport of transporter substrates[23)] by MAAA-1181a (0.1-31.1 μmol/L[24)]) mediated by the above transporters was investigated. MAAA-1181a inhibited the transport of the substrates of OAT1 and OATP1B1 with an $IC_{50}$ of 12.7 and 14.4 μmol/L, respectively. However, MAAA-1181a did not show clear inhibitory effects on the transport of substrates of OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and BSEP.

### 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

In this section, unless otherwise specified, the trastuzumab deruxtecan formulations used were manufactured by Process A [see Section 2.1.3.2]. Vehicles used were as follows: in *in vivo* studies, 10 mmol/L histidine buffer (pH5.8) containing 10 w/v% trehalose and 0.02 w/v% polysorbate 20, 25 mmol/L histidine buffer (pH5.5) containing 9 w/v% sucrose, or 4.2 mmol/L histidine buffer (pH6.0) containing 10 w/v% trehalose and 0.0085 w/v% polysorbate 20; and *in vitro* studies, DMSO.

---

23) The following radiolabeled compounds were used as substrates for the transporters: $^{3}$H-labeled paraaminohippuric acid 1 μmol/L (OAT1); $^{3}$H-labeled digoxin 1 μmol/L (P-gp); $^{3}$H-labeled taurocholic acid 2 μmol/L (BSEP); $^{3}$H-labeled estrone sulfate 50 nmol/L (OAT3) and 0.1 μmol/L (BCRP); $^{14}$C-labeled metformin 10 μmol/L (OCT1, OCT2, MATE1, and MATE2-K); $^{3}$H-labeled estradiol-17β-glucuronide 50 nmol/L (OATP1B1 and OATP1B3).

24) The assays were performed at the following concentrations: at 0.104 to 31.1 μmol/L for OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K; at 0.1 to 30 μmol/L for OAT1, OAT3, P-gp, BCRP, and BSEP.

## 5.1 Single-dose toxicity

Although no single dose toxicity studies were conducted, acute toxicity of trastuzumab deruxtecan was evaluated based on the data following administration of the first dose in repeated intravenous-dose toxicity studies in rats and cynomolgus monkeys. The approximate lethal dose was determined to be >197 mg/kg in rats and >78.8 mg/kg in cynomolgus monkeys (Table 16).

**Table 16. Single-dose toxicity studies**

| Test system | Route of admini-stration | Dose (mg/kg) | Major findings | Approximate lethal dose (mg/kg) | Attached document CTD |
|---|---|---|---|---|---|
| Male/female rats (Sprague Dawley) | Intravenous | 0, 20, 60, and 197 | Acute toxicity was evaluated based on the data from the 6-week repeated intravenous dose toxicity study<br><br>≥20, skin trauma or scabbing<br>197, sparse fur or loss of fur, decreased body weight, and decreased food consumption | >197 | 4.2.3.2-1 |
| Male/female cynomolgus monkeys | Intravenous | 0, 10, 30, and 78.8 | Acute toxicity was evaluated based on the data from the 6-week intermittent intravenous dose toxicity study<br><br>78.8, diarrhea, decreased body weight, and decreased food consumption | >78.8 | 4.2.3.2-2 |

## 5.2 Repeated-dose toxicity

The following repeated intravenous-dose toxicity studies were conducted: 6- and 13 week-studies in cynomolgus monkeys to investigate the toxicity mediated by the binding of trastuzumab deruxtecan to HER2; 6-week study in rats to investigate the toxicity not mediated by the binding of trastuzumab deruxtecan to HER2 (Table 17). Major toxicity findings were divided into the following categories with the details shown below: (a) gastrointestinal, renal, testicular, skin, lymphatic and/or hematopoietic toxicities (cynomolgus monkeys and rats); (b) incisor toxicities (rats); and (c) pulmonary toxicities and effects on cardiac function (cynomolgus monkeys).

(a) These toxicities were found in both species regardless of the binding of trastuzumab deruxtecan, and were therefore considered to be attributable to MAAA-1181a released from trastuzumab deruxtecan.

(b) Likewise, incisor toxicities were also thought to be attributable to MAAA-1181a released from trastuzumab deruxtecan. However, rat incisors, unlike those of humans, continue to grow, which suggests that these changes are probably unique to rodents; therefore, it was considered unlikely that such toxicities would occur in adult patients.

(c) The mechanism of pulmonary toxicity is not clear [see Section 5.R.1]. Effects on cardiac function noted included QT interval prolongation [see Section 5.R.2]. The exposures of trastuzumab deruxtecan ($C_{max}$ and $AUC_{21d}$) at no-observed adverse effect levels (NOAELs) from repeated intravenous-dose toxicity studies in cynomolgus monkeys for 13 weeks and rats for 6 weeks (<3 mg/kg for cynomolgus monkeys; <20 mg/kg for rats) were 88.3 μg/mL ($C_{max}$) and 286 μg·d/mL ($AUC_{21d}$) for cynomolgus monkeys, and 614 μg/mL ($C_{max}$) and 2,508 μg·d/mL ($AUC_{21d}$) for rats.

Compared with the clinical exposures,[25)] these values were <0.68-fold ($C_{max}$) and <0.37-fold ($AUC_{21d}$) in cynomolgus monkeys, and <4.7-fold ($C_{max}$) and <3.3-fold ($AUC_{21d}$) in rats.

**Table 17. Repeated-dose toxicity studies of trastuzumab deruxtecan**

| Test system | Route of admini-stration | Treatment period | Dose (mg/kg/ 3weeks) | Major findings | NOAEL (mg/kg/ 3 weeks) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male/ female rats (Sprague Dawley) | IV | 6 weeks (Q3W) + recovery period 9 weeks | 0<br>20<br>60<br>197 | ≥20, decreased reticulocyte percentage, single cell necrosis of crypt epithelial cells in the small and large intestine, spermatid retention<br><br>≥60, skin ulcer/scabbing/epidermal thickening/dermal fibrosis/inflammatory cell infiltration, mammary gland atrophy, increased urine protein, white discoloration of incisors, decreased white blood cell count, decreased lymphocyte count, decreased eosinophil count, decreased basophil count, decreased neutrophil count, decreased large unstained cell number, increased platelet count, increased inorganic phosphorus in serum, single cell necrosis of thymic lymphocytes, follicular atrophy of submandibular lymph nodes/ileal Peyer's patches, decreased bone marrow erythroblasts, focal villous atrophy of the duodenum, tubular basophilia of the kidney, hyaline casts, single cell necrosis of hair follicles, single cell necrosis of incisor root, focal/multifocal enamel organ degeneration<br><br>197, sparse fur/loss of fur of the skin, decreased body weight, decreased food consumption, decreased urine sperm count (no sperms were detected in some animals), decreased monocyte count, increased urea nitrogen in serum, increased serum creatinine, increased serum potassium, decreased serum sodium, decreased serum chloride, decreased size and weight of testis/epididymis/thymus, decreased myelocytes, inflammatory cell infiltration in the lamina propria and erosion of the mucosa in the duodenum, seminiferous tubular degeneration/atrophy, cell debris and decreased sperm in the duct of epididymis, abnormal dentin formation/hemorrhage in the sub-enamel organ tissue/focal lack of cementum/hypoplasia of the dentin in the incisors, gingivitis<br><br>Reversibility: reversible except for testicular and incisor changes | <20 | 4.2.3.2-1 |

[25)] In the Japanese phase I study (Study J102) conducted in Japanese patients with unresectable or recurrent, HER2-positive breast cancer, the exposures following intravenous administration of trastuzumab deruxtecan 5.4 mg/kg Q3W in Cycle 3 were 130 μg/mL ($C_{max}$) and 764 μg·d/mL ($AUC_{21d}$).

| Test system | Route of admini-stration | Treatment period | Dose (mg/kg/ 3weeks) | Major findings | NOAEL (mg/kg/ 3 weeks) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male/ female cynomol-gus monkeys | IV | 6 weeks (Q3W) + recovery period 6 weeks | 0<br>10<br>30<br>78.8 | Sacrificed moribund[*2]: at 78.8 (F, 1 of 5 animals), diarrhea, abnormal skin color (black-brown, around the forearm/knee), decreased spontaneous activity, decreased body temperature, decreased body weight, decreased food consumption, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, increased serum levels of AST/ALT/CK, increased urea nitrogen in serum, decreased sternal bone marrow erythroblasts/myelocytes, single cell necrosis of crypt epithelial cells in the duodenum, tubular basophilia/tubular epithelial cell growth/anisokaryosis in the proximal tubule/hyaline or cellular casts/hyaline-like material in the interstitium/cellular infiltration of interstitium in the kidney, single cell necrosis of the hair follicles in the skin and injection site, epidermal thickening/pigmentation<br><br>≥10, increased serum levels of AST/ALT, single cell necrosis of crypt epithelial cells in the small and large intestine<br>≥30, single cell necrosis of the hair follicles in the skin and injection site, decreased number of round spermatids in Stages V and VI seminiferous tubules in the testis<br>78.8, diarrhea, abnormal skin color (black-brown, around the shoulder/forearm/thigh/knee), black foci in the skin, white foci in the lung, decreased body weight, decreased food consumption, occult blood-positive in urine, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, decreased reticulocyte percentage, decreased sternal bone marrow erythroblasts/myelocytes, epidermal thickening/pigmentation, tubular basophilia/tubular epithelial cell growth/anisokaryosis in the proximal tubule/hyaline or cellular casts/hyaline material in the interstitium/cellular infiltration of the interstitium, focal interstitial inflammation/foamy alveolar macrophage aggregation/alveolar edema in the lung, abnormal electrocardiogram (PR interval shortening, QT interval prolongation)<br><br>Reversibility: reversible except for changes in the lung (focal interstitial inflammation, foamy alveolar macrophage aggregation, alveolar macrophages with cholesterin clefts, alveolar edema),[*3] the kidney (anisokaryosis in the proximal tubule) and the skin (pigmentation) | <10 | 4.2.3.2-2 |
| Male/ female cynomol-gus monkeys | IV | 6 weeks (Q3W) | 0<br>10[*1]<br>30[*1] | ≥10, increased serum levels of AST/LDH/CK, single cell necrosis of crypt epithelial cells in the small and large intestine<br>30, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, single cell necrosis of the hair follicles in the skin and injection site, decreased sternal bone marrow erythroblasts | <10 | 4.2.3.2-3 |

| Test system | Route of admini-stration | Treatment period | Dose (mg/kg/ 3weeks) | Major findings | NOAEL (mg/kg/ 3 weeks) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male/ female cynomol-gus monkeys | IV | 3 months (Q3W) + recovery period 3 months | 0<br>3[*1]<br>10[*1]<br>30[*1] | ≥3, single cell necrosis of crypt epithelial cells in the small and large intestine<br>≥10, single cell necrosis of the hair follicles in the skin<br>30, abnormal skin color (black-brown), decreased reticulocyte percentage, increased serum levels of AST/LDH/CK, black foci in the skin, white foci in the lung, decreased sternal bone marrow erythroblasts/brown pigment deposition of macrophages, foamy alveolar macrophage aggregation/focal interstitial inflammation/focal alveolar inflammation, anisokaryosis in the renal proximal tubule, epidermal pigmentation of the skin, single cell necrosis of the hair follicles in the injection site, decreased sternal bone marrow myelocytes, brown pigment deposition in liver Kupffer cells/hepatocytes/bile canaliculi, brown pigment deposition in splenic macrophages, decreased number of round spermatids in Stages V and VI seminiferous tubules in the testis<br><br>Reversibility: reversible except for changes in the skin (pigmentation) and kidney (anisokaryosis in the renal proximal tubule) | <3 | 4.2.3.2-4 |

*1, Trastuzumab deruxtecan manufactured by Process B [see Section 2.1.3.2]; *2, it is thought to be caused by deterioration of clinical signs resulting from decreased body weight and food consumption, as well as bone marrow/gastrointestinal toxicities; *3, these findings were observed in females at 30 mg/kg (except for alveolar edema), and males and females at 78.8 mg/kg

### 5.3 Genotoxicity

Since trastuzumab deruxtecan is an ADC, its antibody component is unlikely to interact directly with DNA or other chromosomal components; therefore, genotoxicity studies were performed to evaluate its payload component (MAAA-1181a) using MAAA-1181a monohydrate. The genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay in mammalian cultured cells, and an *in vivo* micronucleus assay in rodents (Table 18). The bacterial reverse mutation assay returned a negative result, while the chromosomal aberration assay and micronucleus assay returned positive results, and it was concluded that trastuzumab deruxtecan induces chromosome aberrations.

The applicant explained that the possibility of inducing chromosomal aberrations cannot be ruled out when trastuzumab deruxtecan 5.4 mg/kg is administered to humans taking into consideration the following findings regarding exposure levels in addition to the above study results: the $AUC_{21d}$ of MAAA-1181a was 30.5 ng·day/mL following administration of trastuzumab deruxtecan 5.4 mg/kg to Japanese patients; the $AUC_{1d}$ was 27.8 ng·d/mL following single-dose intravenous administration of MAAA-1181a to male rats at 3 mg/kg/day, higher than the dose at which micronucleus induction occurred, 0.05 mg/kg/day.

**Table 18. Genotoxicity studies using MAAA-1181a monohydrate**

| Type of study | | Test system | Metabolic activation (treatment) | Concentration[*1] (μg/plate or μg/mL) or dose (mg/kg/day) | Test result | Attached document CTD |
|---|---|---|---|---|---|---|
| *In vitro* | Bacterial reverse mutation assay | Salmonella typhimurium: TA98, TA100, TA1535, TA1537<br>Escherichia coli: WP2*uvrA* | S9−/+ | 0, 313, 625,[*2] 1,250,[*2] 2,500,[*2] 5,000[*2] | Negative | 4.2.3.3.1-1 |
| | Chromosomal aberration assay in mammalian cultured cells | Chinese hamster lung cells (CHL/IU) | S9− (6 hours) | 0, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.8, 1.0 | Positive[*4] | 4.2.3.3.1-2 |
| | | | S9+ (6 hours) | 0, 0.05, 0.1, 0.2, 0.4, 0.8, 1.0, 1.5, 3.0 | | |
| | | | S9− (24 hours) | 0, 0.0125, 0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.3 | | |
| *In vivo* | Micronucleus assay in rodents | Male rats (Sprague Dawley) | | 0,[*3] 0.025, 0.05, 0.1, 0.2 (IV, for 1 day) | Positive[*5] | 4.2.3.3.2-1 |

*1, Calculated as MAAA-1181a; *2, precipitates were observed after incubating for 48 hours; *3, only the vehicle (physiological saline) was administered; *4, structural aberrations were observed at ≥0.1 μg/mL for 6-hour treatment (S9±), and at ≥0.025 μg/mL for 24-hour treatment; *5, increased micronucleated immature erythrocyte count occurred at ≥0.05 mg/kg/day

## 5.4 Carcinogenicity

No carcinogenicity studies were conducted because trastuzumab deruxtecan is an anti-neoplastic agent intended to be used for the treatment of patients with advanced cancer. The applicant explained that the carcinogenic potential of trastuzumab deruxtecan could not be ruled out given that MAAA-1181a is genotoxic [see Section 5.3].

## 5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted because trastuzumab deruxtecan is an anti-neoplastic agent intended to be used for the treatment of patients with advanced cancer, and is expected that it would have adverse effects on embryo-fetal development.

The applicant explained that effects of trastuzumab deruxtecan on fertility and early embryonic development to implantation, pre- and post-natal development, and embryo-fetal development could not be ruled out for several reasons including the following:

- MAAA-1181a is genotoxic [see Section 5.3].
- Findings from the repeated intravenous-dose toxicity studies of trastuzumab deruxtecan or MAAA-1181a indicated effects on quickly dividing cells (e.g., lymphatic/hematopoietic organs, gastrointestinal tract, testis) [see Sections 5.2 and 5.7.2].
- Findings from the repeated intravenous-dose toxicity studies of trastuzumab deruxtecan indicated testicular toxicity in rats and cynomolgus monkeys (seminiferous tubular degeneration/atrophy in rats, not reversible; and decreased number of round spermatids in Stages V and VI seminiferous tubules in the testis, reversible) [see Section 5.2].
- Teratogenicity has been reported in rat and rabbit studies of irinotecan, which is also a topoisomerase I inhibitor and is structurally similar to trastuzumab deruxtecan (*The Clinical Report.* [in Japanese] 1990;24:7275-304, *The Clinical Report.* [in Japanese] 1990;24:7324-36).

- In post-marketing case reports of trastuzumab, trastuzumab treatment during pregnancy has been associated with oligohydramnios, fatal kidney failure in fetuses, aplasia of the lung and other abnormalities (see Package Insert "Herceptin for Intravenous Infusions 60 and 150").
- Excretion in breast milk has been reported in a cynomolgus monkey study of trastuzumab, as well as in a rat study of irinotecan (*Drug Metabol Pharmacokin.* 1991;6:165-167), a drug similar to MAAA-1181a. While it is not known whether trastuzumab deruxtecan or MAAA-1181a is excreted in breast milk, trastuzumab deruxtecan may also be excreted in breast milk [see Section 4.5.2].

### 5.6 Local tolerance

While no local tolerance studies have been conducted, effects of trastuzumab deruxtecan on injection sites were evaluated based on data including the histopathological examination results from the repeated intravenous-dose toxicity studies in rats and cynomolgus monkeys [see Section 5.2]; no findings suggestive of local irritation were noted up to 197 mg/kg/3 weeks, the maximum dose.

### 5.7 Other toxicity studies

#### 5.7.1 Tissue cross-reactivity studies

Tissue cross-reactivity studies were conducted using normal tissue from humans and cynomolgus monkeys (Table 19). The results indicated specific staining of trastuzumab deruxtecan in the plasma membrane of human placenta-related cells.

**Table 19. Tissue cross-reactivity studies of trastuzumab deruxtecan**

| Test system | Method | Major findings | Attached document CTD |
|---|---|---|---|
| Human normal tissue | Frozen sections were treated with trastuzumab deruxtecan 1 or 10 μg/mL, and the binding to the tissue panel (38 tissues) was detected by the indirect ELISA method | At ≥1 μg/mL, specific staining was observed in the plasma membrane or cytoplasm of syncytiotrophoblasts and decidual cells in the placenta. In addition, specific staining in the cytoplasm of epithelial cells was observed in the mammary gland, cervical canal, colon, fallopian tube, kidney, lens fiber of the eye, pancreas, parathyroid gland, pituitary gland, prostate, salivary gland, skin, small intestine, stomach, thymus, thyroid gland, tonsils, ureter, bladder, and endometrium. However, *in vivo,* it is considered that the amount of trastuzumab deruxtecan that will reach the cytoplasm directly is negligible. Therefore, it was concluded that binding to cytoplasm alone is a reaction not biologically relevant. | 4.2.3.7.7-1 |
| Cynomolgus monkey normal tissue | Frozen sections were treated with trastuzumab deruxtecan 1 or 10 μg/mL, and the binding to the tissue (10 tissues*) was detected by the indirect ELISA method | No specific staining in the plasma membrane was observed in the tissues studied. | 4.2.3.7.7-2 |

*, Bone marrow, brain, heart, gastrointestinal tract, kidney, liver, lung, skin, spleen, and testis

#### 5.7.2 Repeated-dose toxicity studies of MAAA-1181a

Four-week repeated intravenous-dose toxicity studies of MAAA-1181a monohydrate were conducted in rats and cynomolgus monkeys (Table 20). Key toxicity findings were toxicity of the gastrointestinal tract, lymphatic/hematopoietic organs, and cornea (rats and cynomolgus monkeys); and cardiac toxicity (in the sacrificed moribund cynomolgus monkey). Unlike animals treated with trastuzumab deruxtecan

[see Section 5.2], (a) MAAA-1181a-treated animals did not show kidney, skin, testicular, or incisor toxicities; on the other hand, (b) additional toxicity findings, namely, corneal and cardiac toxicities, were observed.

The applicant explained that based on the toxicity and situation of trastuzumab deruxtecan or MAAA-1181a exposure, continuous exposure to trastuzumab deruxtecan or the released payload MAAA-1181a may have led to the toxicities listed in (a) above; and the toxicities in (b) may have been caused by the higher exposures to MAAA-1181a compared with those when trastuzumab deruxtecan was administered in the study.

**Table 20. Repeated-dose toxicity studies of MAAA-1181a**

| Test system | Route of admini-stration | Treatment period | Dose[*1] (mg/kg/ week) | Major findings | NOAEL (mg/kg/ day) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male/ female rats (Sprague Dawley) | IV | 4 weeks (QW) + recovery period 4 weeks | 0, 3, 10, 30 | ≥3, decreased body weight gain, decreased food consumption, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, decreased reticulocyte percentage, decreased white blood cell count, decreased lymphocyte count, decreased basophil count, decreased neutrophil count, decreased eosinophil count, decreased monocyte count, increased serum glucose, decreased thymus weight, decreased bone marrow erythroblasts/myelocytes, single cell necrosis of thymic lymphocytes, follicular atrophy of ileal Peyer's patches/submandibular lymph nodes, single cell necrosis of crypt epithelial cells in the small and large intestine, villous atrophy of the duodenum, single cell necrosis of corneal epithelial cells<br><br>30, thymic atrophy, crypt epithelial cell regeneration accompanied by expansion of cecal crypts<br><br>Reversibility, reversible | <3 | 4.2.3.7.7-3 |
| Male/ female cynomol-gus monkeys | IV | 4 weeks (QW) + recovery period 4 weeks | 0, 1, 3, 12 | Sacrificed moribund,[*2] at 12 (M, 1 of 5animals), died,[*2] at 12 (F, 1 of 5 animals), vomiting, diarrhea, lateral position, decreased body temperature, pale oral mucosa, decreased contact response, decreased body weight, decreased food consumption, no food consumption, decreased hematocrit, decreased lymphocyte count, increased serum levels of AST/ALT, decreased serum levels of Na/Cl, myocardial degeneration/necrosis (only in the animal sacrificed moribund), decreased bone marrow erythroblasts/myelocytes, atrophy of follicles and periarterial lymphatic sheath in the spleen, follicular atrophy of the mesenteric lymph nodes/ileac Peyer's patches, single cell necrosis/focal necrosis/increased mitosis of hepatocytes, canalicular bile thrombi, dilatation of bile canaliculi, brown pigment deposition in Kupffer cells, crypt epithelial cell regeneration/single cell necrosis/crypt expansion in the small and large intestine<br><br>≥1, decreased reticulocyte percentage, follicular atrophy of the spleen/mesenteric lymph nodes/ileac Peyer's patches, single cell necrosis of thymic lymphocytes<br><br>≥3, vomiting, body weight decreased, increased serum AST<br><br>12, abnormal stool, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, decreased lymphocyte count, increased platelet count, shortening/prolongation of activated partial thromboplastin time, increased serum levels of ALT/inorganic phosphorus/potassium, single cell necrosis of hepatocytes, single cell necrosis of crypt epithelial cells in the small intestine, single cell necrosis of the corneal epithelium<br><br>Reversibility, reversible | <1 | 4.2.3.7.7-4 |

*1, Calculated as MAAA-1181a; *2, it is thought to be caused by deterioration of clinical signs accompanied by decreased body weight or food consumption, and bone marrow/gastrointestinal toxicities resulting from MAAA-1181a treatment

### 5.7.3 Repeated-dose toxicity studies of MAAL-9001

Six-week repeated intravenous-dose toxicity studies of MAAL-9001 were conducted in rats and cynomolgus monkeys (Table 21). In these studies, no toxicities were observed.

**Table 21. Repeated-dose toxicity studies of MAAL-9001**

| Test system | Route of administration | Treatment period | Dose (mg/kg/3 weeks) | Major findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male/female rats (Sprague Dawley) | IV | 6 weeks (Q3W) | 0, 197 | No toxicity changes | 197 | 4.2.3.7.7-5 |
| Male/female cynomolgus monkeys | IV | 6 weeks (Q3W) | 0, 78.8 | No toxicity changes | 78.8 | 4.2.3.7.7-6 |

### 5.7.4 Photosafety

A phototoxicity study of MAAA-1181a monohydrate was conducted (Table 22). The findings from the *in vitro* study indicated phototoxicity, while those of the *in vivo* study indicated no phototoxicity. Adverse event data from the clinical studies indicated no phototoxicity-related safety concerns. On the basis of the above, it was concluded that trastuzumab deruxtecan is unlikely to be phototoxic.

**Table 22. Photosafety studies of MAAA-1181a**

| Type of study | Test system | Method*1 | Major findings | Attached document CTD |
|---|---|---|---|---|
| Phototoxicity | Mouse fibroblast cell line Balb/c 3T3 | 0.195-25 μg/mL (under UV-A*2 irradiation)<br>0.195-25 μg/mL (no UV-A*2 irradiation) | May cause phototoxicity (calculated mean photo effect, 0.432) | 4.2.3.7.7-7 |
| | Male pigmented rats (Iar:Long-Evans) | A single dose of 0, 1 or 3 mg/kg was administered intravenously; 30 minutes after the administration, UV-A*3 was irradiated to evaluate photo irritation and other factors | None | 4.2.3.7.7-8 |

*1, Calculated as MAAA-1181a; *2, UV-A (5 J/cm$^2$) irradiation for approximately 50 minutes; *3, UV-A (10 J/cm$^2$) irradiation for approximately 60 minutes

### 5.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 the toxicity of trastuzumab deruxtecan is acceptable.

### 5.R.1 Effects on the lungs

In cynomolgus monkey studies, at ≥30 mg/kg in the 6-week repeated intravenous dose toxicity study and at 30 mg/kg in the 3-month repeated intravenous dose toxicity study, pulmonary toxicities (e.g., focal interstitial inflammation, foamy alveolar macrophage aggregation, alveolar macrophages with cholesterin clefts, and alveolar edema) occurred, with the incidence and seriousness being dose-dependent [see Section 5.2]. Prolongation of the treatment period did not increase seriousness, and the toxicities were reversible after the recovery period in the 3-month repeated intravenous dose toxicity study [see Section 5.2]. However, because of the high incidence of interstitial lung disease (ILD) in the

clinical studies [see Section 7.R.3.1] and other factors, PMDA asked the applicant to explain the mechanism of pulmonary toxicity caused by trastuzumab deruxtecan.

The applicant's response:
While the mechanism of pulmonary toxicity caused by trastuzumab deruxtecan has not been clarified at this point, the information provided below has already been reported. Furthermore, ILD occurred at a high incidence in the clinical studies, and fatal ILD events have also been reported. Therefore, cautionary advice regarding ILD will be given in the package insert or other materials [see Section 7.R.3.3].

- No toxicity changes were observed in the repeated intravenous dose toxicity studies of MAAL-9001 in rats and cynomolgus monkeys [see Section 5.7.3]. In addition, no toxicity changes were observed in the 6-month repeated intravenous dose toxicity study of trastuzumab in cynomolgus monkeys (see Review Report of Herceptin for Intravenous Infusion 150, dated March 8, 2001).
- Positive responses have been detected in bronchial epithelial cells in cynomolgus monkeys, as with humans, by immunohistochemistry (IHC) with anti-HER2 antibody; however, the sites of pulmonary toxicity did not coincide with the sites of anti-HER2 antibody binding sites.
- Positive responses have been detected in alveolar macrophages, blood vessels, and blood components in the surrounding tissue (including alveolar edema fluid) by IHC with anti-MAAA-1181a antibody in the lung tissue of cynomolgus monkeys treated with trastuzumab deruxtecan; however, no clear positive responses were detected in the other components.
- In the repeated intravenous dose toxicity studies of MAAA-1181a in rats and cynomolgus monkeys, no pulmonary toxicity occurred [see Section 5.7.2]. Furthermore, while the blood concentrations were high immediately following intravenous administration of MAAA-1181a to rats and cynomolgus monkeys, the clearance was high and the half-life was as short as 0.04 to 0.2 days.

PMDA's discussion:
Since serious ILD events and fatal ILD events have been reported in the clinical studies, the mechanism of pulmonary toxicity by trastuzumab deruxtecan treatment is clinically important information. Therefore, it was concluded that the mechanism should further be examined, and new information should be appropriately provided to healthcare professionals as soon as it becomes available.

The safety of trastuzumab deruxtecan in clinical use will be discussed in Section 7.R.3.3.

### 5.R.2 Effects on the heart

The applicant's explanation about QT interval prolongation and other findings noted in the repeated intravenous dose toxicity studies of trastuzumab deruxtecan:
In the 6-week repeated intravenous dose toxicity study of trastuzumab deruxtecan in cynomolgus monkeys, changes such as QT interval prolongation occurred in 1 animal in the high dose group (78.8 mg/kg) [see Section 5.2]. However, it is unlikely that QT interval prolongation will occur in association with the clinical use of trastuzumab deruxtecan for several reasons including the following: QT prolongation was minor in degree; no effects on the cardiovascular system were reported in the safety

pharmacology study of MAAA-1181a [see Section 3.2.2]; and no effects on cardiac function (e.g., electrocardiographic parameters, cardiac function test, and cardiac troponin) were noted at 30 mg/kg in the 3-month repeated intravenous dose toxicity study of trastuzumab deruxtecan in cynomolgus monkeys [see Section 5.2].

PMDA's discussion:
The applicant's explanation is acceptable from a toxicological viewpoint taking into account that in the 3-month repeated intravenous dose toxicity study of trastuzumab deruxtecan in cynomolgus monkeys, no effects of trastuzumab deruxtecan on the heart including QT interval prolongation were observed at 30 mg/kg, which is equivalent to 7.7-fold ($C_{max}$) and 6.5-fold ($AUC_{21d}$) the clinical exposure[25)] [see Section 5.2].

The safety of trastuzumab deruxtecan in clinical use will be discussed in Section 7.R.3.7.

## 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

#### 6.1.1 Analytical methods

##### 6.1.1.1 Assay of trastuzumab deruxtecan

Trastuzumab deruxtecan in human serum was determined by ECL using solid phased [redacted], [redacted]-labeled [redacted], and [redacted]-labeled [redacted], with a lower limits of quantitation of 400 ng/mL.

##### 6.1.1.2 Assay of unconjugated MAAA-1181a

The unconjugated MAAA-1181a in human serum was determined by LC-MS/MS, with a lower limits of quantitation of 10 pg/mL.

##### 6.1.1.3 Assay of anti-trastuzumab deruxtecan antibodies

Anti-drug antibodies in human serum were measured by bridging ECL using solid phased [redacted], [redacted]-labeled trastuzumab deruxtecan, and [redacted]-labeled trastuzumab deruxtecan, with a detection sensitivity of 46.3 ng/mL.

#### 6.1.2 Changes made to manufacturing process during the development of drug substance and drug product

During the development, changes were made to the manufacturing processes of the drug substance and drug product [see Sections 2.1.3.2 and 2.2.3]. Table 23 shows formulations used in the clinical studies submitted for the present application. When changes were made to the manufacturing processes of the drug substance or drug product, comparability was evaluated in terms of the quality attributes. The evaluation results demonstrated the comparability of the drug substance or drug product before and after the manufacturing process change [see Sections 2.1.3.2 and 2.2.3].

**Table 23. Formulations used in the clinical studies**

| Manufacturing process of formulation | Study |
|---|---|
| Process 1 | Global phase I (Study J101) |
| Process 2 | Global phase I (Study J101), global phase II (Study U201) |
| Process 3 | Japanese phase I (Study J102), foreign phase I (Study A103), global phase I (Study A104), global phase II (Study U201) |

## 6.2 Clinical pharmacology

The PK of trastuzumab deruxtecan and MAAA-1181a in patients with cancer was investigated when trastuzumab deruxtecan was administered alone or in combination with itraconazole or ritonavir.

In the following clinical studies, patients who had prior treatment of trastuzumab or T-DM1 were also enrolled, and total MAAL-9001 was detected in the serum of some patients before the start of administration of trastuzumab deruxtecan. For this reason, it is difficult to properly evaluate the PK of total MAAL-9001 following administration of trastuzumab deruxtecan based on the results of these studies, and therefore the details of the results are not discussed here.

### 6.2.1 Global clinical studies

#### 6.2.1.1 Global phase I study (CTD 5.3.3.2-1, Study J101 [ongoing since September 2015, data cut-off on February 1, 2019])

An open-label, uncontrolled study was conducted in 292 patients with unresectable or recurrent HER2-positive breast cancer, etc. to investigate the PK and other aspects of trastuzumab deruxtecan (286 of 292 patients were included in the PK analyses). The study consisted of Part 1, the dose escalation phase, and Part 2, the dose expansion phase. The dosage regimen was trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg Q3W as administered intravenously for Part 1 (dose escalation), and trastuzumab deruxtecan 5.4 or 6.4 mg/kg Q3W as administered intravenously for Part 2 (dose expansion), and serum trastuzumab deruxtecan concentrations and other parameters were studied.

Tables 24 and 25 show PK parameters of trastuzumab deruxtecan and MAAA-1181a following administration of the first dose of trastuzumab deruxtecan. The $C_{max}$ and AUC of trastuzumab deruxtecan generally increased in a dose-proportional manner.

Of the 289 subjects whose ADAs were measured after administration of the first dose of trastuzumab deruxtecan, ADAs were detected in 1 subject.[26)]

[26)] In this subject, ADAs were detected at baseline and after the first dose of trastuzumab deruxtecan.

**Table 24. PK parameters of trastuzumab deruxtecan and MAAA-1181a (Part 1[*4])**

| Analyte | Dose (mg/kg) | n | $C_{max}$ (μg/mL[*2]) | $t_{max}$[*1] (h) | $AUC_{last}$ (μg·day/mL[*3]) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| Trastuzu-mab deruxtecan | 0.8 | 3 | 22.9 ± 3.76 | 1.95 (1.62, 1.98) | 51.7 ± 13.1 | 2.18 ± 0.671 | 15.0 ± 2.89 | 45.0 ± 8.96 |
| | 1.6 | 3 | 36.2 ± 4.98 | 4.03 (1.87, 4.08) | 116 ± 58.7 | 3.07 ± 1.22 | 16.1 ± 9.27 | 58.3 ± 10.0 |
| | 3.2 | 3 | 78.2 ± 16.1 | 4.12 (1.95, 6.88) | 325 ± 142 | 4.23 ± 1.24 | 11.3 ± 6.52 | 56.8 ± 14.4 |
| | 5.4 | 6 | 127 ± 17.2 | 2.02 (1.87, 2.07) | 544 ± 165 | 6.03 ± 0.603 | 10.1 ± 3.90 | 75.2 ± 24.2 |
| | 6.4 | 6 | 181 ± 33.1 | 2.06 (1.50, 3.97) | 901 ± 155 | 7.33 ± 1.64 | 6.41 ± 1.12 | 58.6 ± 11.0 |
| | 8.0 | 5 | 224 ± 41.0 | 1.97 (1.70, 6.80) | 996 ± 229 | 6.44 ± 0.793 | 7.60 ± 1.73 | 62.1 ± 14.0 |
| MAAA-1181a | 0.8 | 3 | 1.17 ± 0.757 | 6.77 (6.75, 22.25) | 4.84 ± 1.89 | 2.50 ± 0.579 | — | — |
| | 1.6 | 3 | 1.72 ± 0.193 | 6.98 (6.82, 24.05) | 8.53 ± 2.15 | 3.48 ± 1.09 | — | — |
| | 3.2 | 3 | 5.69 ± 0.530 | 6.88 (4.00, 6.88) | 24.0 ± 7.58 | 4.68 ± 0.969 | — | — |
| | 5.4 | 6 | 10.8 ± 7.56 | 5.38 (3.83, 23.75) | 40.6 ± 19.8 | 6.11 ± 0.811 | — | — |
| | 6.4 | 6 | 6.80 ± 1.72 | 6.83 (4.05, 7.15) | 31.0 ± 5.11 | 6.28 ± 1.17 | — | — |
| | 8.0 | 5 | 9.65 ± 2.56 | 6.80 (2.07, 7.00) | 40.3 ± 5.66 | 6.45 ± 1.56 | — | — |

Mean ± standard deviation; "—", not calculated; *1, median (range); *2, values for MAAA-1181a are expressed in ng/mL; *3, values for MAAA-1181a are expressed in ng·day/mL; *4, the trastuzumab deruxtecan formulation (manufactured by Process 1) containing the drug substance manufactured by Process A [see Section 2.1.3.2] was used

**Table 25. PK parameters of trastuzumab deruxtecan and MAAA-1181a (Parts 2a through 2e)**

| Analyte | Dose (mg/kg) | Part | n | $C_{max}$ (μg/mL[*2]) | $t_{max}$[*1] (h) | $AUC_{last}$ (μg·day/mL[*3]) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 5.4 | 2a: HER2-positive breast cancer[*13] | 48 | 126 ± 37.7 | 2.00 (1.50, 6.85) | 559 ± 178 | 5.52 ± 1.23 | 10.2 ± 3.95 | 68.3 ± 15.5 |
| | | 2b: HER2-positive gastric cancer[*13] | 17 | 113 ± 30.0 | 2.03 (1.58, 4.08) | 542 ± 163 | 6.18 ± 1.18 | 10.1 ± 3.69 | 78.0 ± 21.2 |
| | | 2c: HER2 low-expressing breast cancer[*13] | 20 | 133 ± 18.3 | 2.16 (1.50, 7.07) | 581 ± 180 | 5.28 ± 1.49[*4] | 9.72 ± 2.55[*4] | 63.4 ± 12.9[*4] |
| | 6.4 | 2a: HER2-positive breast cancer[*13] | 50 | 170 ± 53.6 | 2.08 (1.53, 7.05) | 785 ± 228 | 6.00 ± 1.22[*5] | 8.38 ± 3.19[*5] | 62.3 ± 13.3[*5] |
| | | 2b: HER2-positive gastric cancer[*13] | 23 | 116 ± 21.1 | 1.95 (1.53, 7.00) | 507 ± 126 | 5.90 ± 1.57[*6] | 12.3 ± 4.14[*6] | 89.5 ± 14.6[*6] |
| | | 2c: HER2 low-expressing breast cancer[*13] | 19 | 155 ± 33.2 | 2.00 (1.50, 6.67) | 693 ± 178 | 5.79 ± 1.01[*7] | 9.22 ± 3.37[*7] | 65.6 ± 14.9[*7] |
| | | 2d: HER2-expressing (other than breast or gastric cancer) or *HER2*-mutated solid tumors[*13] | 59 | 150 ± 30.3 | 2.02 (1.50, 7.20) | 631 ± 184[*8] | 5.61 ± 1.29[*8] | 10.5 ± 4.01[*8] | 70.5 ± 16.7[*8] |
| | | 2e: HER2-expressing breast cancer[*14] | 21 | 155 ± 21.4 | 2.05 (1.62, 7.23) | 693 ± 102 | 5.46 ± 1.02 | 8.74 ± 1.59 | 63.4 ± 8.95 |
| MAAA-1181a | 5.4 | 2a: HER2-positive breast cancer[*13] | 48 | 8.22 ± 6.21 | 5.78 (1.93, 75.75) | 35.1 ± 24.3 | 5.58 ± 1.29[*9] | — | — |
| | | 2b: HER2-positive gastric cancer[*13] | 17 | 9.62 ± 7.20 | 6.92 (3.78, 24.07) | 45.6 ± 44.4 | 6.28 ± 1.29[*10] | — | — |
| | | 2c: HER2 low-expressing breast cancer[*13] | 20 | 9.93 ± 3.99 | 4.11 (2.05, 23.48) | 40.2 ± 17.0 | 5.34 ± 1.08[*4] | — | — |
| | 6.4 | 2a: HER2-positive breast cancer[*13] | 50 | 9.76 ± 4.47 | 6.90 (3.75, 71.83) | 43.1 ± 15.2 | 5.57 ± 1.10[*11] | — | — |
| | | 2b: HER2-positive gastric cancer[*13] | 23 | 9.66 ± 7.52 | 6.88 (3.83, 166.37) | 43.2 ± 26.5 | 5.09 ± 1.19[*6] | — | — |
| | | 2c: HER2 low-expressing breast cancer[*13] | 19 | 12.2 ± 3.45 | 6.75 (3.83, 7.25) | 40.1 ± 9.89 | 5.41 ± 0.961[*10] | — | — |
| | | 2d: HER2-expressing (other than breast or gastric cancer) or *HER2*-mutated solid tumors[*13] | 59 | 13.3 ± 8.74 | 6.83 (3.58, 23.78) | 49.1 ± 45.0[*8] | 5.25 ± 1.31[*12] | — | — |
| | | 2e: HER2-expressing breast cancer[*14] | 21 | 14.4 ± 5.50 | 6.92 (3.92, 7.23) | 46.6 ± 16.3 | 5.34 ± 1.22[*4] | — | — |

Mean ± standard deviation; "—", not calculated; *1, median (range); *2, values for MAAA-1181a are expressed in ng/mL; *3, values for MAAA-1181a are expressed in ng·day/mL; *4, n = 19; *5, n = 49; *6, n = 22; *7, n = 17; *8, n = 58; *9, n = 43; *10, n = 16; *11, n = 46; *12, n = 55; *13, the trastuzumab deruxtecan formulation (manufactured by Process 1) containing the drug substance manufactured by Process A [see Section 2.1.3.2] was used; *14, the trastuzumab deruxtecan formulation (manufactured by Process 2) containing the drug substance manufactured by Process B [see Section 2.1.3.2] was used

### 6.2.2 Foreign clinical studies

#### 6.2.2.1 Foreign phase I study (CTD 5.3.3.2-2, Study A103 [ongoing since April 2018, data cut-off on September 14, 2018])

An open-label, uncontrolled study was conducted in 12 patients previously treated with trastuzumab and who had HER2-positive[27)] (a) unresectable or recurrent breast cancer, or (b) unresectable advanced or recurrent gastric cancer, to investigate the PK and other aspects of trastuzumab deruxtecan (all 12 subjects were included in the PK analysis). Trastuzumab deruxtecan 6.4 mg/kg was administered intravenously Q3W in 21-day cycles, and serum trastuzumab deruxtecan concentrations and other parameters were studied.

Table 26 shows PK parameters of trastuzumab deruxtecan and MAAA-1181a.

In 12 subjects, following administration of the first dose of trastuzumab deruxtecan, ADAs were measured, and no ADAs were detected.

**Table 26. PK parameters of trastuzumab deruxtecan and MAAA-1181a**

| Analyte | n | Cycle | $C_{max}$ (μg/mL*2) | $t_{max}$*1 (h) | $C_{trough}$ (μg/mL) | $AUC_{21day}$ (μg·day/mL*3) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 12 | 1 | 157 ± 19.1 | 2.08 (1.88, 4.08) | 6.21 ± 2.94 | 631 ± 173 | 5.68 ± 0.881 | 10.4 ± 4.33 | 81.2 ± 18.7 |
| | 12 | 3 | 163 ± 19.5*4 | 2.02*4 (0.55, 4.00) | 13.3 ± 4.60 | 991 ± 109*4 | 7.82 ± 1.14*4 | 6.53 ± 0.750*4 | 66.0 ± 6.96*4 |
| MAAA-1181a | 12 | 1 | 11.9 ± 3.79 | 4.08 (3.75, 7.08) | 0.288 ± 0.145 | 36.1 ± 9.71 | 5.94 ± 1.43 | — | — |
| | 12 | 3 | 9.01 ± 1.36*4 | 4.00*4 (1.95, 7.12) | 0.495 ± 0.0904 | 41.3 ± 5.06*4 | 6.77 ± 0.798*5 | — | — |

Mean ± standard deviation; *1, median (range); *2, values for MAAA-1181a are expressed in ng/mL; *3, values for MAAA-1181a are expressed in ng·day/mL; *4, n = 10; *5, n = 9

### 6.2.3 Drug interaction studies

#### 6.2.3.1 Drug interactions with itraconazole or ritonavir (CTD 5.3.3.4-1, Study A104 [ongoing since January 2018, data cut-off on September 26, 2018])

An open-label, uncontrolled study was conducted in 40 patients with HER2-expressing[28)] advanced solid tumors to investigate the effects of itraconazole (CYP3A inhibitor) or ritonavir (dual CYP3A/OATP1B inhibitor) on the PK of trastuzumab deruxtecan and MAAA-1181a (26 of 40 subjects were included in the PK analysis). Trastuzumab deruxtecan was administered in 21-day cycles as follows:

Cohort 1: Trastuzumab deruxtecan 5.4 mg/kg was administered intravenously Q3W; ritonavir 200 mg was administered orally BID after meals between Day 17 of Cycle 2 and Day 21 of Cycle 3.

Cohort 2: Trastuzumab deruxtecan 5.4 mg/kg was administered intravenously Q3W; itraconazole 200 mg was administered orally BID after meals on Day 17 of Cycle 2, and itraconazole 200 mg was administered orally QD after a meal between Day 18 of Cycle 2 and Day 21 of Cycle 3.

27) Patients with score 3+ cancer by IHC or *in situ* hybridization (ISH)-positive cancer were eligible.
28) Patients with score 1+, 2+, or 3+ cancer by IHC, or ISH-positive cancer were eligible.

For the PK parameters of trastuzumab deruxtecan, the geometric mean ratio [90% confidence interval (CI)] of trastuzumab deruxtecan with itraconazole to trastuzumab deruxtecan alone was 1.03 [0.96, 1.09] for $C_{max}$, and 1.11 [1.07, 1.15] for $AUC_{17day}$; the geometric mean ratio [90% CI] of trastuzumab deruxtecan with ritonavir to trastuzumab deruxtecan alone was 1.05 [0.98, 1.13] for $C_{max}$ and 1.19 [1.14, 1.25] for $AUC_{17day}$. For the PK parameters of MAAA-1181a, the geometric mean ratio [90% CI] of trastuzumab deruxtecan with itraconazole to trastuzumab deruxtecan alone was 1.04 [0.92, 1.18] for $C_{max}$ and 1.18 [1.11, 1.25] for $AUC_{17day}$; and the geometric mean ratio [90% CI] of trastuzumab deruxtecan with ritonavir to trastuzumab deruxtecan alone was 0.99 [0.85, 1.14] for $C_{max}$ and 1.22 [1.08, 1.37] for $AUC_{17day}$. In addition to these results, regarding the incidence of serious adverse events, Grade ≥3 adverse events, or adverse events leading to treatment discontinuation, there was no clear increase in these events associated with co-administration with CYP3A inhibitors or OATP1B inhibitors; therefore, the applicant explained that no cautionary advice would be necessary regarding co-administration with the above inhibitors.

### 6.2.4 Relationship between exposure and change in QT/QTc interval

The relationship between serum trastuzumab deruxtecan concentrations and QT interval corrected with Fridericia's formula (QTcF) was investigated using a linear mixed effects model based on the data from 49 subjects enrolled in the Japanese phase I study (Study J102) whose serum trastuzumab deruxtecan concentrations and electrocardiographic measurements were able to be taken at the same time point.

Following administration of trastuzumab deruxtecan 6.4 mg/kg intravenously Q3W, change from baseline in QTcF (ΔQTcF) [90% CI] (ms) at $C_{max}$[29)] of trastuzumab deruxtecan was estimated to be 1.3 [−1.2, 3.8] for Cycle 1 and 1.4 [−1.1, 3.9] for Cycle 3; and that of MAAA-1181a was estimated to be 2.7 [0.1, 5.3] for Cycle 1 and 0.7 [−1.4, 2.7] for Cycle 3. The upper limits of the two-sided 90% CI for ΔQTcF were estimated to be lower than 10 ms at all timepoints.

On the basis of the above, the applicant explained that trastuzumab deruxtecan is unlikely to cause QT interval prolongation when used clinically.

### 6.2.5 PPK analyses

Population pharmacokinetic (PPK) analyses of trastuzumab deruxtecan and MAAA-1181a were performed based on the PK data of trastuzumab deruxtecan and MAAA-1181a (n = 639; 11,495 timepoints [serum trastuzumab deruxtecan concentration] and 11,527 timepoints [serum MAAA-1181a concentration]) from the Japanese phase I study (Study J102), global phase I studies (Studies J101 and A104), global phase II study (Study U201), and foreign phase I study (Study A103) using a nonlinear mixed effects model (software, NONMEM Version 7.3). The PK of trastuzumab deruxtecan was described by a two-compartment model with a first-order elimination process, while the PK of MAAA-

29) The mean $C_{max}$ of trastuzumab deruxtecan was 179 μg/mL for Cycle 1 and 154 μg/mL for Cycle 3, and that of MAAA-1181a was 12.6 ng/mL for Cycle 1 and 9.60 ng/mL for Cycle 3.

1181a was described by a one-compartment model with a time-varying release rate constant ($K_{rel}$) and a first-order elimination process.

In the analyses, the following covariates were tested for their effects on elimination clearance of intact DS-8201a ($CL_{intact}$), central volume of distribution ($V_1$), peripheral volume of distribution ($V_2$), and intact DS-8201a inter-compartmental clearance ($Q_{intact}$) of trastuzumab deruxtecan: body weight, age, sex, albumin, baseline tumor size, country of enrollment, race, formulation, lactate dehydrogenase (LDH), HER2 expression, tumor type, or prior HER2-targeted therapies.[30)] For the effects on elimination clearance of released drug, MAAA-1181a ($CL_{drug}$), released drug (MAAA-1181a) volume of distribution ($V_{drug}$), and $K_{rel}$ of MAAA-1181a, the following covariates were tested: body weight, age, sex, baseline tumor size, country of enrollment, race, formulation, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, degree of hepatic impairment, creatinine clearance (CLcr), and co-administration with itraconazole/ritonavir. The following significant covariates were identified for trastuzumab deruxtecan: body weight, albumin, baseline tumor size, country of enrollment, and sex on $CL_{intact}$; body weight and sex on $V_1$; and country of enrollment on $V_2$. The following significant covariates were identified for MAAA-1181a: body weight, total bilirubin, AST, co-administration with itraconazole/ritonavir on $CL_{drug}$; age and formulation on $V_{drug}$; and none on $K_{rel}$. None of the covariates had significant effects on the exposure ($C_{max}$, $C_{min}$, and AUC at steady state) of trastuzumab deruxtecan or MAAA-1181a; therefore, the applicant explained that these covariates are unlikely to have clinically significant effects on the PK of trastuzumab deruxtecan or MAAA-1181a.

### 6.2.6 Exposure-efficacy/safety relationship

#### 6.2.6.1 Exposure-efficacy relationship

On the basis of the data obtained from Studies J101 and U201, the relationship between each exposure metrics[31)] ($C_{max}$, $C_{min}$, and AUC in Cycle 1 and at steady state, and $C_{avg}$ up to the onset of an event) of trastuzumab deruxtecan/MAAA-1181a and each efficacy endpoint (objective response rate, progression free survival [PFS], and duration of response) was investigated. The objective response rate tended to increase with increase in $C_{avg}$ of trastuzumab deruxtecan. In contrast, no clear relationship was observed between exposure ($C_{max}$, $C_{min}$, and AUC) of trastuzumab deruxtecan/MAAA-1181a and efficacy endpoint (PFS and duration of response).

#### 6.2.6.2 Exposure-safety relationship

On the basis of the data obtained from Studies J101, J102, A103, A104, and U201, the relationship between each exposure metrics[31)] ($C_{max}$, $C_{min}$, and AUC in Cycle 1 and at steady state, and $C_{avg}$ up to the onset of an event) of trastuzumab deruxtecan/MAAA-1181a and each safety endpoint (adverse events leading to treatment discontinuation, adverse events leading to dose reduction, adverse events leading to dose interruption, Grade ≥3 adverse events, serious adverse events, adverse events of special interest [i.e., anaemia, neutrophil count decreased, platelet count decreased, and ILD] of any grade and Grade

30) Therapies with HER2-targeting agents such as trastuzumab, T-DM1, pertuzumab, and lapatinib. The same shall apply hereinafter.

31) The exposure metrics were estimated by PPK analyses [see Section 6.2.5].

≥3, and Grade ≥2 left ventricular ejection fraction [LVEF] decreased) was investigated. The following trends were observed between the exposure of trastuzumab deruxtecan/MAAA-1181a and adverse events:

- The incidence of adverse events leading to treatment discontinuation and ILD of any grade tended to increase with increasing AUC of trastuzumab deruxtecan at steady state.
- The incidence of Grade ≥3 ILD and Grade ≥2 LVEF decreased tended to increase with increasing $C_{max}$ of trastuzumab deruxtecan at steady state.
- The incidence of adverse events leading to dose reduction, adverse events leading to dose interruption, Grade ≥3 adverse events, serious adverse events, anaemia of any grade and Grade ≥3, neutrophil count decreased of any grade and Grade ≥3, and platelet count decreased of any grade and Grade ≥3 tended to increase with increasing $C_{avg}$ of MAAA-1181a.

### 6.2.7 Effects of deteriorated renal function on PK of trastuzumab deruxtecan

No clinical studies have been conducted to evaluate the PK and other parameters of trastuzumab deruxtecan in patients with renal impairment.

The applicant explained that taking into account the factors including the findings below, deteriorated renal function is unlikely to affect the PK of trastuzumab deruxtecan or MAAA-1181a.

- Since trastuzumab deruxtecan is thought to be eliminated through the degradation pathway mediated by target antigen binding and a nonspecific protein degradation pathway, deteriorated renal function is unlikely to affect the exposure of trastuzumab deruxtecan.
- In PPK analyses, CLcr was not identified as a significant covariate for trastuzumab deruxtecan or MAAA-1181a [see Section 6.2.5].
- In the PPK analyses [see Section 6.2.5], the $C_{max}$ and AUC (geometric mean) of MAAA-1181a at steady state following administration of trastuzumab deruxtecan 5.4 mg/kg were estimated for each category of baseline renal function.[32)] In patients with normal renal function (n = 238), mild renal impairment (n = 206), and moderate renal impairment (n = 58[33)]), the $C_{max}$ was 4.66 ng/mL (normal), 4.25 ng/mL (mild), and 4.34 ng/mL (moderate), and AUC was 29.5 ng·day/mL (normal), 27.2 ng·day/mL (mild), and 27.8 ng·day/mL (moderate), indicating no clear differences in the PK of MAAA-1181a between the renal function categories.

32) Patients were classified based on CLcr measurements: normal renal function, ≥90 mL/min; mild renal impairment, 60 to 89 mL/min; moderate renal impairment, 30 to 59 mL/min; severe renal impairment, 15 to 29 mL/min.
33) One patient with severe renal impairment was included in this group.

### 6.2.8 Differences in PK of trastuzumab deruxtecan between Japanese and non-Japanese populations

The applicant explained that taking into account the factors including the findings below, there is no clear differences in the PK of trastuzumab deruxtecan and MAAA-1181a between Japanese and non-Japanese populations.

- In the global phase I study (Study J101), no clear differences in the PK parameters of trastuzumab deruxtecan and MAAA-1181a were found between Japanese and non-Japanese patients following intravenous administration of trastuzumab deruxtecan 5.4 mg/kg (Table 27).
- The PPK analyses identified country of enrollment as a significant covariate on $CL_{intact}$ and $V_2$ of trastuzumab deruxtecan [see Section 6.2.5]; however, the geometric mean ratio of Japanese to non-Japanese for estimated steady state $C_{max}$ was 0.931 (trastuzumab deruxtecan) and 0.965 (MAAA-1181a), and that for estimated steady state AUC was 0.991 (trastuzumab deruxtecan) and 1.02 (MAAA-1181a), suggesting that PK is similar between Japanese and non-Japanese populations.

**Table 27. PK parameters of trastuzumab deruxtecan and MAAA-1181a following administration of the first dose of trastuzumab deruxtecan**

| Analyte | Japanese/non-Japanese patients | n | $C_{max}$ (μg/mL*2) | $t_{max}$*1 (h) | $AUC_{last}$ (μg·day/mL*3) | $t_{1/2}$ (day) |
|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | Japanese | 26 | 120 ± 25.2 | 2.05 (1.75, 7.07) | 563 ± 120 | 5.78 ± 1.21 |
| | Non-Japanese | 45 | 134 ± 35.5 | 2.00 (1.50, 6.92) | 573 ± 202 | 5.32 ± 1.32*4 |
| MAAA-1181a | Japanese | 26 | 8.05 ± 4.67 | 6.92 (3.82, 23.8) | 36.9 ± 16.4 | 6.04 ± 1.16 |
| | Non-Japanese | 45 | 9.51 ± 6.52 | 4.08 (1.93, 75.8) | 37.8 ± 25.4 | 5.21 ± 1.15*5 |

Mean ± standard deviation; *1, median (range); *2, values for MAAA-1181a are expressed in ng/mL; *3, values for MAAA-1181a are expressed in ng·day/mL; *4, n = 44; *5, n = 39

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Effects of ADAs on PK of trastuzumab deruxtecan

The applicant's explanation about the effects of trastuzumab deruxtecan in the specimen on the measurement of ADAs:

The concentration of trastuzumab deruxtecan in the specimen that will not affect measurements of ADAs against trastuzumab deruxtecan by the assay method for ADAs [see Section 6.1.1.3] was 53.3 μg/mL. Taking into account that serum trastuzumab deruxtecan concentrations in specimens (n = 2,797) that were measured for ADAs in the clinical studies were ≤53.3 μg/mL, except for 20 specimens, it is unlikely that trastuzumab deruxtecan in specimen may have had an impact on the measurement of ADAs.

The applicant's explanation about the effects of ADAs on the PK of trastuzumab deruxtecan:

The incidence of ADAs in patients with unresectable or recurrent HER2-positive breast cancer, etc. who were treated with trastuzumab deruxtecan was investigated in the Japanese phase I study (Study J102), global phase I studies (Studies J101 and A104), global phase II study (Study U201), and foreign phase I study (Study A103). Of the 640 subjects who were tested for ADAs after administration of the first dose of trastuzumab deruxtecan, ADAs were detected in 7 subjects[34] (1.1%).

[34] Including 5 subjects in whom ADAs were detected at baseline and after administration of trastuzumab deruxtecan.

A comparison of serum trastuzumab deruxtecan concentrations between ADA-positive subjects and ADA-negative subjects indicated no clear differences between the ADA-positive and negative subjects (Table 28).

**Table 28. Serum trastuzumab deruxtecan concentrations (μg/mL)**

| Study | Dose | Measurement timepoint | ADAs | | | |
|---|---|---|---|---|---|---|
| | | | n | Positive | n | Negative |
| U201 | 5.4 mg/kg | Before dosing on Day 1 of Cycle 2 | 3 | 4.40 ± 2.59 | 172 | 5.40 ± 5.67 |
| | 5.4 mg/kg | Before dosing on Day 1 of Cycle 4 | 2 | 9.35 ± 0.856 | 161 | 10.8 ± 9.25 |

Mean ± standard deviation

PMDA's discussion:

PMDA largely accepted the applicant's explanation above. However, given the very limited number of subjects who tested positive for ADAs following administration of trastuzumab deruxtecan, it is difficult to determine the effect of ADAs on the PK of trastuzumab deruxtecan based on the current data. It was concluded that information regarding the effects of ADAs on the PK of trastuzumab deruxtecan should be continuously collected and whenever new information becomes available, it should be provided to healthcare professionals in an appropriate manner.

### 6.R.2 Use of trastuzumab deruxtecan in patients with hepatic impairment

The applicant's explanation about the use of trastuzumab deruxtecan in patients with hepatic impairment:

On the basis of the factors presented below, no adjustment to the dose of trastuzumab deruxtecan is required for patients with mild or moderate hepatic impairment. On the other hand, taking into account that no clinical study data in patients with severe hepatic impairment are available; and that biliary excretion or hepatic metabolism is involved in the elimination of MAAA-1181a [see Sections 4.4.2 and 4.5.1], it is appropriate to include cautionary statement to the effect that caution should be exercised when using trastuzumab deruxtecan in patients with severe hepatic impairment.

- Steady state $C_{max}$ and AUC (geometric mean) of MAAA-1181a were estimated for each of baseline hepatic function categories[35]: normal hepatic function (n = 283), mild hepatic impairment (n = 215), and moderate hepatic impairment (n = 4[36]). The $C_{max}$ was 4.40 ng/mL (normal), 4.51 ng/mL (mild), and 5.31 ng/mL (moderate); and the AUC was 27.5 ng·day/mL (normal), 29.5 ng·day/mL (mild), and 31.3 ng·day/mL (moderate), indicating no clear differences across different hepatic function categories.
- Of the patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101 or U201, the incidence of adverse events in patients with normal hepatic function (n = 132) was compared with that in patients with mild hepatic impairment (n = 99). The incidence of adverse events in any grade was 99.2% (normal) and 100% (mild); Grade ≥3 adverse events, 54.5% (normal) and 42.4% (mild); serious adverse events, 20.5% (normal) and 19.2% (mild); and adverse

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

36) Including 3 subjects with unknown hepatic function status.

events leading to dose reduction, 22.0% (normal) and 11.1% (mild). The results suggested no clear differences in the incidence of adverse events between patients with normal hepatic function and mild hepatic impairment.

- Although the number of patients with moderate hepatic impairment who have received trastuzumab deruxtecan is limited, no adverse events leading to treatment discontinuation or dose reduction occurred in patients who were enrolled in Study U201 and received a total of 4 doses of trastuzumab deruxtecan 5.4 mg/kg, and a causal relationship was denied by the investigator for the serious adverse event of hyperkalaemia which occurred on the 34th day following administration of the final dose.

PMDA's discussion:

PMDA largely accepted the applicant's explanation above. However, given the importance of information on the PK of trastuzumab deruxtecan and MAAA-1181a in patients with hepatic impairment to ensure the proper use of trastuzumab deruxtecan, it was concluded that the information should be continuously collected, and whenever new information becomes available, it should be provided to healthcare professionals in an appropriate manner.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 5 studies as summarized in Table 29: 1 Japanese phase I study, 2 global phase I studies, 1 global phase II study, and 1 foreign phase I study.

**Table 29. 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 | Japan | J102 | I | Unresectable or recurrent HER2-expressing[*1] breast cancer | 51 | Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W | PK |
| | Global | J101 | I | Part 1<br>Patients with unresectable or recurrent breast cancer, and patients with unresectable advanced or recurrent gastric cancer<br>Part 2<br>2a, Patients with unresectable or recurrent HER2-positive[*2] breast cancer previously treated with T-DM1<br>2b, Patients with HER2-positive[*3] gastric cancer previously treated with trastuzumab<br>2c, Patients with unresectable or recurrent HER2 low-expressing[*4] breast cancer<br>2d, Patients with HER2-expressing[*5] advanced solid tumors (other than breast/gastric cancer), and *HER2*-mutated advanced solid tumors<br>2e, Patients with unresectable or recurrent HER2-expressing[*1] breast cancer | Part 1<br>27<br>Part 2<br>2a, 103<br>2b, 41<br>2c, 40<br>2d, 60<br>2e, 21 | Part 1<br>Trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg IV infusion Q3W<br>Part 2<br>Trastuzumab deruxtecan 5.4 or 6.4 mg/kg IV infusion Q3W | Efficacy<br>Safety<br>Tolerability<br>PK |
| | | A104 | I | Patients with HER2-expressing[*1] advanced solid tumors | Cohort 1, 17<br>Cohort 2, 23 | Cohort 1<br>Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W in combination with ritonavir[*6]<br>Cohort 2<br>Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W in combination with itraconazole[*7] | PK |
| | | U201 | II | Patients with unresectable or recurrent HER2-positive[*2] breast cancer previously treated with T-DM1 | Part 1<br>PK stage, 65<br>Dose-finding stage, 54<br>Part 2<br>2a, 130<br>2b, 4 | Part 1<br>PK stage,<br>Trastuzumab deruxtecan 5.4, 6.4, or 7.4 mg/kg IV infusion Q3W<br>Dose-finding stage,<br>Trastuzumab deruxtecan 5.4 or 6.4 mg/kg IV infusion Q3W<br>Part 2<br>Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W | Efficacy<br>Safety<br>PK |
| | Foreign | A103 | I | Patients with HER2-positive[*2] cancer shown below, previously treated with trastuzumab<br>• unresectable or recurrent breast cancer<br>• unresectable advanced or recurrent gastric cancer | 12 | Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W | PK |

*1, Defined as tumors scored as 1+, 2+, or 3+ by IHC, or ISH-positive; *2, defined as tumors scored as 3+ by IHC, or ISH-positive; *3, defined as tumors scored as 3+ by IHC, or tumors scored as 2+ by IHC and ISH-positive; *4, defined as tumors scored as 2+ by IHC and ISH-negative, tumors scored as 1+ by IHC and ISH-negative, or tumors scored as 1+ by IHC and ISH not-evaluated; *5, defined as expression detected by IHC, ISH, next generation sequencing (NGS), or other method; *6, ritonavir 200 mg was administered orally BID between Day 17 of Cycle 2 and Day 21 of Cycle 3 of trastuzumab deruxtecan treatment; *7, itraconazole 200 mg was administered orally BID on Day 17 of Cycle 2, and 200 mg orally QD between Day 18 of Cycle 2 and Day 21 of Cycle 3 of trastuzumab deruxtecan treatment

The following sections provide an outline of 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." Pharmacokinetic results from studies are described in Section "6.2 Clinical pharmacology."

## 7.1 Evaluation data

### 7.1.1 Clinical pharmacology studies

The applicant submitted the results from the 3 clinical pharmacology studies conducted in patients with HER2-expressing[37] or HER2-positive[38] (a) unresectable or recurrent breast cancer, (b) unresectable advanced or recurrent gastric cancer, and (c) advanced solid tumors [see Section 6.2]. During the treatment period or within 47 days of the last dose of trastuzumab deruxtecan in these studies, an adverse event led to death in 1 subject (Study A104, 1 of 40 subjects), and the cause of death was disease progression.

#### 7.1.1.1 Japanese phase I study (CTD 5.3.4.2-1, Study J102 [ongoing since January 2018, data cut-off on December 5, 2018])

#### 7.1.1.2 Global phase I study (CTD 5.3.3.4-1, Study A104 [ongoing since January 2018, data cut-off on September 26, 2018])

#### 7.1.1.3 Foreign phase I study (CTD 5.3.3.2-2, Study A103 [ongoing since April 2018, data cut-off on September 14, 2018])

### 7.1.2 Global studies

#### 7.1.2.1 Global phase I study (CTD 5.3.3.2-1, Study J101 [ongoing since September 2015, data cut-off on February 1, 2019])

An open-label, uncontrolled study was conducted at 14 study centers in 2 countries including Japan to assess the efficacy, safety, PK and other aspects of trastuzumab deruxtecan in patients with unresectable or recurrent HER2-positive breast cancer, etc.[39] (target sample size: Part 1, 18 subjects; Part 2a, 100 subjects; Part 2b, 40 subjects; Part 2c, 40 subjects; Part 2d, 60 subjects; and Part 2e, 20 subjects).

The dosage regimens were as follows: in Part 1 (dose escalation), trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg intravenously Q3W; and in Parts 2a through 2e (dose expansion), trastuzumab

---

37) Defined as tumors scored as 1+, 2+, or 3+ by IHC, or ISH-positive.

38) Defined as tumors scored as 3+ by IHC, or ISH-positive.

39) The target populations enrolled in Study J101 are shown below by part. Parts 1, 2c, 2d, and 2e enrolled patients refractory or intolerant to standard lines of treatment.
- Part 1: Patients with unresectable or recurrent breast cancer, and patients with unresectable advanced or recurrent gastric cancer.
- Part 2a: Patients with unresectable or recurrent HER2-positive (scored as 3+ by IHC or ISH-positive) breast cancer previously treated with T-DM1.
- Part 2b: Patients with HER2-positive (scored as 3+ by IHC, or scored as 2+ by IHC and ISH-positive) gastric cancer previously treated with trastuzumab.
- Part 2c: Patients with unresectable or recurrent HER2 low-expressing (scored as 2+ by IHC and ISH-negative, scored as 1+ by IHC and ISH-negative, or scored as 1+ by IHC and ISH not-evaluated) breast cancer.
- Part 2d: Patients with HER2-expressing (detected by e.g., IHC, ISH, NGS) advanced solid tumors (other than breast/gastric cancer), and *HER2*-mutated advanced solid tumors.
- Part 2e: Patients with unresectable or recurrent HER2-expressing (scored as 1+, 2+, or 3+ by IHC, or ISH-positive) breast cancer.

deruxtecan 5.4 or 6.4 mg/kg intravenously Q3W. Treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

All 103 subjects (including 48 Japanese subjects) enrolled in Part 2a were included in the efficacy analyses for Part 2a. In Part 2a, 49 subjects (including 19 Japanese subjects) were assigned to the 5.4 mg/kg group, and 54 subjects (including 29 Japanese subjects) were assigned to the 6.4 mg/kg group. Of the 292 subjects enrolled in the study, 3 subjects who did not receive trastuzumab deruxtecan were excluded, and the remaining 289 subjects (including 178 Japanese subjects) were included in the safety analyses. Among these subjects, the number of patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg as the initial dose was 50 (including 21 Japanese subjects).

The first 21 days after the start of trastuzumab deruxtecan treatment in Part 1 was defined as the dose limiting toxicity (DLT) assessment period. No DLTs were observed, and the maximum tolerated dose (MTD) was not determined.

The primary purpose of this study was to evaluate safety and tolerability. As the efficacy endpoints, which are the primary purpose of Part 2, objective response rate and other measures of efficacy by independent central review (ICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1 were specified. No statistical hypothesis testing-based assessment was included in the efficacy evaluation.

Table 30 shows the results of objective response rate by ICR according to RECIST ver1.1, the efficacy endpoint for the study (data cut-off on February 1, 2019).

**Table 30. Best overall response and objective response rate**
**(RECIST ver.1.1, Part 2a, 5.4 mg/kg, efficacy analysis set, by ICR, data cut-off on February 1, 2019)**

| Best overall response | Number of subjects (%) | |
|---|---|---|
| | Entire study population n = 49 | Japanese subpopulation n = 19 |
| CR | 2 (4.1) | 2 (10.5) |
| PR | 22 (44.9) | 9 (47.4) |
| SD | 19 (38.8) | 6 (31.6) |
| PD | 4 (8.2) | 1 (5.3) |
| NE | 2 (4.1) | 1 (5.3) |
| Response (CR + PR) (objective response rate % [95% CI*]) | 24 (49.0% [34.4, 63.7]) | 11 (57.9% [33.5, 79.7]) |

*, Clopper-Pearson method

During the treatment period and within 28 days of the last dose of trastuzumab deruxtecan, deaths occurred in 10 of 289 subjects (3.5%), including 5 deaths in Japanese subjects. Three of the 10 subjects died from disease progression. Other causes of death were respiratory failure (3 subjects); pneumonitis (1 subject); mechanical ileus (1 subject); pneumonia aspiration (1 subject); and disseminated intravascular coagulation, febrile neutropenia, and hepatic function abnormal (1 subject). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for respiratory failure (2 subjects); pneumonitis (1 subject); and disseminated intravascular coagulation, febrile neutropenia, and

hepatic function abnormal (1 subject). Adverse events that were identified as causes of death in Japanese subjects were mechanical ileus (1 subject); pneumonia aspiration (1 subject); and disseminated intravascular coagulation, febrile neutropenia, and hepatic function abnormal (1 subject). A causal relationship to trastuzumab deruxtecan could not be ruled out for disseminated intravascular coagulation, febrile neutropenia, and hepatic function abnormal (1 subject).

Of the patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg, deaths occurred in 3 of 50 subjects (6.0%). One of the 3 subjects died from disease progression. The cause of death for the other 2 subjects was respiratory failure, and a causal relationship to trastuzumab deruxtecan could not be ruled out in 1 of these subjects. (One Japanese subject died, and the cause of death was disease progression.)

#### 7.1.2.2 Global phase II study (CTD 5.3.5.2-1, Study U201 [ongoing since October 2017, data cut-off on March 21, 2019])

An open-label, uncontrolled study was conducted at 72 study centers in 8 countries including Japan to assess the efficacy, safety, and PK of trastuzumab deruxtecan in patients with unresectable or recurrent HER2-positive[40] breast cancer previously treated with T-DM1[41] (target sample size: Part 1 PK stage,[42] 60 subjects; Part 1 dose-finding stage,[43] 60 subjects; Part 2a, 100 subjects; and Part 2b, 15 subjects).

The dosage regimens were as follows: trastuzumab deruxtecan intravenously Q3W, at 5.4, 6.4, or 7.4 mg/kg in the PK stage, at 5.4 or 6.4 mg/kg in the dose-finding stage, and at 5.4 mg/kg in Parts 2a and 2b. Treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

Of the 253 subjects enrolled in this study (PK stage, 65; dose-finding stage, 54; Part 2a, 130; and Part 2b, 4), 180 subjects who were enrolled in Part 1 or Part 2a, and assigned to the 5.4 mg/kg group were included in the Enrolled Analysis Set; and 167 subjects in the Enrolled Analysis Set who received at least 1 dose of trastuzumab deruxtecan and had target lesions identified by ICR were included in the Response Evaluable Set. The Enrolled Analysis Set and Response Evaluable Set were included in the efficacy analyses (Japanese patients were 30 in Enrolled Analysis Set and 26 in Response Evaluable Set). All 253 subjects (including 56 Japanese subjects) enrolled in this study received trastuzumab deruxtecan and were included in the safety analyses. Of the subjects included in the safety analyses, 184 subjects (including 30 Japanese subjects) received an initial dose of 5.4 mg/kg trastuzumab deruxtecan.

The primary endpoint of the study was objective response rate by ICR according to RECIST ver1.1.

---

40) Defined as tumors scored as 3+ by IHC, or ISH-positive.
41) Parts 1 and 2a enrolled patients who had tumor progression after treatment with T-DM1, Part 2b enrolled patients who discontinued T-DM1 treatment for reasons other than tumor progression.
42) The PK stage study was performed for the purpose evaluating PK.
43) The dose-finding stage was performed to determine the recommended dosage for Part 2 by analyzing exposure-response using data from this stage.

Tables 31 and 32 show the results of objective response rate by ICR according to RECIST ver1.1, the primary efficacy endpoint of the study. The lower limit of the 95% CI exceeded the pre-specified objective response rate of 20%[44] (data cut-off on March 21, 2019).

**Table 31. Best overall response and objective response rate (RECIST ver.1.1, Enrolled Analysis Set, by ICR, data cut-off on March 21, 2019)**

| Best overall response | Number of subjects (%) | |
|---|---|---|
| | Entire study population N = 180 | Japanese subpopulation n = 30 |
| CR | 8 (4.4) | 1 (3.3) |
| PR | 101 (56.1) | 19 (63.3) |
| SD | 66 (36.7) | 8 (26.7) |
| PD | 3 (1.7) | 1 (3.3) |
| NE | 2 (1.1) | 1 (3.3) |
| Response (CR + PR) (objective response rate % [95% CI*]) | 109 (60.6% [53.0, 67.8]) | 20 (66.7% [47.2, 82.7]) |

*, Clopper-Pearson method

**Table 32. Best overall response and objective response rate (RECIST ver.1.1, Response Evaluable Set, by ICR, data cut-off on March 21, 2019)**

| Best overall response | Number of subjects (%) | |
|---|---|---|
| | Entire study population N = 167 | Japanese subpopulation n = 26 |
| CR | 6 (3.6) | 0 |
| PR | 101 (60.5) | 19 (73.1) |
| SD | 55 (32.9) | 5 (19.2) |
| PD | 3 (1.8) | 1 (3.8) |
| NE | 2 (1.2) | 1 (3.8) |
| Response (CR + PR) (objective response rate % [95% CI*]) | 107 (64.1% [56.3, 71.3]) | 19 (73.1% [52.2, 88.4]) |

*, Clopper-Pearson method

The objective response rate (%) [95% CI] in the Enrolled Analysis Set was as follows: in the entire study population, 64.0% [49.2, 77.1] (32 of 50 subjects) in Part 1 and 59.2% [50.3, 67.8] (77 of 130 subjects) in Part 2a; in the Japanese subpopulation, 62.5% [35.4, 84.8] (10 of 16 subjects) in Part 1 and 71.4% [41.9, 91.6] (10 of 14 subjects) in Part 2a. The objective response rate (%) [95% CI] in the Response Evaluable Set was as follows: in the entire study population, 66.0% [50.7, 79.1] (31 of 47 subjects) in Part 1 and 63.3% [54.1, 71.9] (76 of 120 subjects) in Part 2a; in the Japanese subpopulation, 64.3% [35.1, 87.2] (9 of 14 subjects) in Part 1 and 83.3% [51.6, 97.9] (10 of 12 subjects) in Part 2a.

During the treatment period and within 47 days of the last dose of trastuzumab deruxtecan, deaths occurred in 9 of 253 subjects (3.6%), and no deaths occurred in Japanese subjects. Four of the 9 subjects died from disease progression. Other causes of death were pneumonitis (1 subject); shock haemorrhagic (1 subject); general physical health deterioration (1 subject); pneumonia (1 subject); and acute organ

[44] In a foreign phase III study conducted to compare the efficacy and safety of T-DM1 with the efficacy and safety of treatment of physician's choice in patients with unresectable or recurrent HER2-positive breast cancer previously treated with ≥2 HER2-targeted regimens, the objective response rate for the physician's choice group was 9% (*Lancet Oncol.* 2014;15:689-99). On the basis of the objective response rate from this study, an objective response rate of 20% was pre-specified.

failure, acute hepatic failure, and acute kidney injury (1 subject). A causal relationship to trastuzumab deruxtecan could not be ruled out for pneumonitis in 1 subject.

Of the patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg, deaths occurred in 7 of 184 subjects (3.8%), and no deaths occurred in Japanese subjects. Three of the 7 subjects died from disease progression. The causes of death for the other 4 subjects were shock haemorrhagic (1 subject); general physical health deterioration (1 subject); pneumonia (1 subject); and acute organ failure, acute hepatic failure, and acute kidney injury (1 subject). A causal relationship to trastuzumab deruxtecan was denied for all these events.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Review strategy

Of the evaluation data submitted, PMDA concluded that Study U201, the global phase II study that was conducted to assess the efficacy and safety of trastuzumab deruxtecan in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1, is the pivotal study in evaluating the efficacy of trastuzumab deruxtecan. Therefore, PMDA decided to conduct efficacy and safety review mainly focusing on Study U201. PMDA also decided to conduct safety review mainly focusing on Study J101, as well as Study U201, the global phase I study that was conducted to assess efficacy, safety, PK, and other aspects in patients with unresectable or recurrent HER2-positive breast cancer.

### 7.R.2 Efficacy

Based on the following discussions, PMDA concluded that trastuzumab deruxtecan has a certain degree of efficacy in the treatment of patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1.

#### 7.R.2.1 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint for Study U201 and the efficacy of trastuzumab deruxtecan in the treatment of patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 in the study:

It has been reported that when response is achieved, the quality of life (QOL) and performance status of patients with unresectable or recurrent breast cancer can be expected to improve as a result of tumor shrinkage (*Nat Rev Clin Oncol*. 2015;12:358-70). Achieving response is considered clinically meaningful, and therefore, objective response rate was selected as the primary endpoint for Study U201.

In Study U201, the objective response rate (%) [95% CI] was reported as follows: in the Enrolled Analysis Set, 60.6% [53.0, 67.8] for the entire study population and 66.7% [47.2, 82.7] for the Japanese subpopulation; in the Response Evaluable Set, 64.1% [56.3, 71.3] for the entire study population and 73.1% [52.2, 88.4] for the Japanese subpopulation [see Section 7.1.2.2]. The objective response rate and other indicators are clinically meaningful for the study population of Study U201. Although the limited number of Japanese subjects studied precluded a strict evaluation of the efficacy of trastuzumab

deruxtecan in Japanese patients, similarly to the entire study population, response was achieved in the Japanese subpopulation as well. Table 33 shows the objective response rate for trastuzumab deruxtecan in patients with or without prior pertuzumab therapy, and by the number of prior regimens for unresectable or recurrent breast cancer. Tumor responses to trastuzumab deruxtecan treatment were confirmed, independent of prior therapies, in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1. All 253 patients enrolled in Study U201 had previously been treated with both T-DM1 and trastuzumab.

**Table 33. Best overall response and objective response rate by prior therapy (RECIST ver.1.1, Enrolled Analysis Set, by ICR, data cut-off on March 21, 2019)**

| Best overall response | Prior pertuzumab therapy | | Number of lines of prior therapies for unresectable or recurrent breast cancer*1 | |
|---|---|---|---|---|
| | Yes | No | 2 | ≥3 |
| | n = 118 | n = 62 | n = 17 | n = 163 |
| CR | 7 (5.9) | 1 (1.6) | 0 | 8 (4.9) |
| PR | 68 (57.6) | 33 (53.2) | 13 (76.5) | 88 (54.0) |
| SD | 41 (34.7) | 25 (40.3) | 4 (23.5) | 62 (38.0) |
| PD | 1 (0.8) | 2 (3.2) | 0 | 3 (1.8) |
| NE | 1 (0.8) | 1 (1.6) | 0 | 2 (1.2) |
| Response (CR + PR) (objective response rate % [95%CI*2]) | 75 (63.6% [54.2, 72.2]) | 34 (54.8% [41.7, 67.5]) | 13 (76.5% [50.1, 93.2]) | 96 (58.9% [50.9, 66.5]) |

*1, Excluding hormone therapies; *2, Clopper-Pearson method

In patients who received trastuzumab deruxtecan 5.4 mg/kg in Part 2a of Study J101, the objective response rate (%) [95% CI] by ICR according to RECIST ver1.1 was 49.0% [34.4, 63.7] (24 of 49 subjects) for the entire study population and 57.9% [33.5, 79.7] (11 of 19 subjects) for the Japanese subpopulation [see Section 7.1.2.1].

In addition to the results from Studies U201 and J101 shown above, taking into account several factors including the following, trastuzumab deruxtecan is expected to have efficacy in the treatment of patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1.

- In a foreign phase III study conducted to compare the efficacy and safety of lapatinib plus capecitabine versus capecitabine alone in patients with unresectable or recurrent breast cancer that had progressed after being treated with regimens that included trastuzumab, a taxane, and an anthracycline, the objective response rate by ICR was 22% in the lapatinib plus capecitabine group (*N Engl J Med.* 2006;355:2733-43).
- In a foreign phase III study conducted to compare the efficacy and safety of T-DM1 with the efficacy and safety of treatment of physician's choice[45)] in patients with unresectable or recurrent HER2-positive breast cancer previously treated with ≥2 HER2-targeted regimens, the investigator-assessed objective response rate for the physician's choice group was 9% (*Lancet Oncol.* 2014; 15: 689-99).

45) Of the 185 subjects, 1 subject received T-DM1 in error, while 153 subjects received HER2-targeted therapy in combination with chemotherapy, and 31 subjects received chemotherapy alone.

- Trastuzumab deruxtecan contains a drug payload, which has a mechanism of action different from that of T-DM1, a HER2-targeted ADC[46], and has characteristics including (a) a high DAR [see Section 3.R.1], (b) high stability in blood [see Section 4.4.1], and (c) high membrane permeability of MAAA-1181a, exerting an antitumor effect also on neighboring tumor cells not bound by trastuzumab deruxtecan [see Section 3.1.5.2.2]. Therefore, trastuzumab deruxtecan is expected to have efficacy in patients with unresectable or recurrent breast cancer refractory to T-DM1 and other existing HER2-targeted therapies.

PMDA's discussion:

Because the relationship between overall survival (OS), a true endpoint for patients with unresectable or recurrent HER2-positive breast cancer, and the objective response rate is not clear, the effect of trastuzumab deruxtecan on prolongation of life in the patient population is difficult to evaluate based on the objective response results, the primary endpoint of Study U201. Nevertheless, the applicant's explanation about the efficacy of trastuzumab deruxtecan above is still reasonable. PMDA concluded that taking into account the factor described below, objective response rates and other data from Study U201 demonstrated that trastuzumab deruxtecan has a certain degree of efficacy in the treatment of patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 including Japanese patients.

- The Clinical Practice Guidelines for Breast Cancer in Japan recommend that patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 continue HER2-targeted therapies; however, it has been suggested that the strength of the recommendation and the supporting evidence is rather weak and it is not generally accepted that a standard therapy has been established.

### 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 considered that adverse events that require particular attention when trastuzumab deruxtecan is used in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 are ILD, myelosuppression, infusion related reaction (IRR), hepatic dysfunction, and cardiac disorder, and that patients should be carefully monitored for these adverse events when using trastuzumab deruxtecan.

Although the use of trastuzumab deruxtecan requires particular caution for the adverse events mentioned above, PMDA concluded that patients should be able to tolerate trastuzumab deruxtecan provided that appropriate steps including monitoring and control of adverse events and dose modification are taken by a physician with sufficient knowledge and experience in cancer chemotherapy, and that safety management measures can be ensured by utmost attention and control measures for serious adverse events including ILD.

46) While DM1, the drug payload of T-DM1, is a microtubule polymerization inhibitor, MAAA-1181a, the drug payload of trastuzumab deruxtecan, is a topoisomerase inhibitor.

### 7.R.3.1 Safety profiles of trastuzumab deruxtecan

The applicant's explanation about the safety of trastuzumab deruxtecan based on the safety data from Studies U201 and J101:

Table 34 summarizes the safety data from Studies U201 and J101.

**Table 34. Summary of safety data (Studies U201 and J101)**

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 | | J101 | |
| | HER2-positive breast cancer 5.4 mg/kg n = 184 | HER2-positive breast cancer 5.4-7.4 mg/kg n = 253 | HER2-positive breast cancer 5.4 mg/kg n = 50 | Solid tumors 0.8-8.0 mg/kg n = 289 |
| All adverse events | 183 (99.5) | 252 (99.6) | 50 (100) | 288 (99.7) |
| Grade ≥3 adverse events | 94 (51.1) | 144 (56.9) | 23 (46.0) | 168 (58.1) |
| Adverse events leading to death | 9 (4.9) | 12 (4.7) | 3 (6.0) | 12 (4.2) |
| Serious adverse events | 36 (19.6) | 50 (19.8) | 11 (22.0) | 73 (25.3) |
| Adverse events leading to treatment discontinuation | 15 (8.2) | 29 (11.5) | 7 (14.0) | 52 (18.0) |
| Adverse events leading to dose interruption | 57 (31.0) | 85 (33.6) | 21 (42.0) | 128 (44.3) |
| Adverse events leading to dose reduction | 37 (20.1) | 67 (26.5) | 5 (10.0) | 65 (22.5) |

In Study U201, in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg, adverse events of any grade with an incidence of ≥20% were nausea (142 subjects, 77.2%); alopecia and fatigue (88 subjects each, 47.8%); vomiting (83 subjects, 45.1%); constipation (63 subjects, 34.2%); decreased appetite (53 subjects, 28.8%); diarrhoea (49 subjects, 26.6%); anaemia (47 subjects, 25.5%); and neutrophil count decreased (37 subjects, 20.1%). Grade ≥3 adverse events with an incidence of ≥5% were neutrophil count decreased (18 subjects, 9.8%); nausea and neutropenia (14 subjects each, 7.6%); anaemia (12 subjects, 6.5%); and fatigue (10 subjects, 5.4%). A serious adverse event with an incidence of ≥2% was vomiting (4 subjects, 2.2%). An adverse event leading to treatment discontinuation with an incidence of ≥2% was pneumonitis (7 subjects, 3.8%). Adverse events leading to dose interruption with an incidence of ≥2% were neutrophil count decreased (14 subjects, 7.6%); neutropenia (11 subjects, 6.0%); anaemia (7 subjects, 3.8%); white blood cell count decreased and platelet count decreased (4 subjects each, 2.2%). Adverse events leading to dose reduction with an incidence of ≥2% were fatigue (6 subjects, 3.3%); nausea (5 subjects, 2.7%); and blood bilirubin increased (4 subjects, 2.2%). No adverse events led to death with an incidence of ≥2%.

Of all the patients who received any dose level of trastuzumab deruxtecan in Study U201, adverse events of any grade with an incidence of ≥20% were nausea (195 subjects, 77.1%); alopecia (124 subjects, 49.0%); fatigue (123 subjects, 48.6%); vomiting (109 subjects, 43.1%); constipation (90 subjects, 35.6%); decreased appetite (80 subjects, 31.6%); anaemia (77 subjects, 30.4%); diarrhoea and neutrophil count decreased (66 subjects each, 26.1%); and white blood cell count decreased (60 subjects, 23.7%). Grade ≥3 adverse events with an incidence of ≥5% were neutrophil count decreased (34 subjects, 13.4%); anaemia and fatigue (23 subjects each, 9.1%); nausea and neutropenia (20 subjects each, 7.9%); and white blood cell count decreased (17 subjects, 6.7%). Serious adverse events with an incidence of

≥2% were vomiting and nausea (5 subjects each, 2.0%). Adverse events leading to treatment discontinuation with an incidence of ≥2% were pneumonitis (9 subjects, 3.6%) and interstitial lung disease (8 subjects, 3.2%). Adverse events leading to dose interruption with an incidence of ≥2% were neutrophil count decreased (21 subjects, 8.3%); neutropenia (16 subjects, 6.3%); anaemia (12 subjects, 4.7%); white blood cell count decreased (7 subjects, 2.8%); and fatigue (6 subjects, 2.4%). Adverse events leading to dose reduction with an incidence of ≥2% were fatigue (15 subjects, 5.9%); nausea (10 subjects, 4.0%); neutrophil count decreased (7 subjects, 2.8%); and blood bilirubin increased (5 subjects, 2.0%). No adverse events led to death with an incidence of ≥2%.

In Study J101, in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg, adverse events of any grade with an incidence of ≥20% were nausea (43 subjects, 86.0%); vomiting (28 subjects, 56.0%); fatigue (24 subjects, 48.0%); decreased appetite and anaemia (23 subjects each, 46.0%); alopecia (19 subjects, 38.0%); diarrhoea and constipation (18 subjects each, 36.0%); platelet count decreased (15 subjects, 30.0%); cough (14 subjects, 28.0%); neutrophil count decreased (12 subjects, 24.0%); pyrexia and oedema peripheral (10 subjects each, 20.0%). Grade ≥3 adverse events with an incidence of ≥5% were neutrophil count decreased (6 subjects, 12.0%); anaemia (5 subjects, 10.0%); and respiratory failure (4 subjects, 8.0%). An adverse event leading to death in ≥2 subjects was respiratory failure (2 subjects, 4.0%). Serious adverse events that occurred in ≥2 subjects were respiratory failure (4 subjects, 8.0%); pneumonitis (3 subjects, 6.0%); and pneumonia (2 subjects, 4.0%). Adverse events leading to treatment discontinuation in ≥2 subjects were pneumonitis (3 subjects, 6.0%). Adverse events leading to dose interruption in ≥2 subjects were neutrophil count decreased (5 subjects, 10.0%); nausea, pyrexia, and platelet count decreased (2 subjects each, 4.0%). An adverse event leading to dose reduction in ≥2 subjects was nausea (2 subjects, 4.0%).

Of all the patients who received any dose level of trastuzumab deruxtecan in Study J101, adverse events of any grade with an incidence of ≥20% were nausea (222 subjects, 76.8%); decreased appetite (168 subjects, 58.1%); vomiting (133 subjects, 46.0%); alopecia (120 subjects, 41.5%); anaemia (117 subjects, 40.5%); fatigue (111 subjects, 38.4%); diarrhoea (102 subjects, 35.3%); constipation and platelet count decreased (100 subjects each, 34.6%); neutrophil count decreased (91 subjects, 31.5%); white blood cell count decreased (82 subjects, 28.4%); AST increased (63 subjects, 21.8%); malaise (62 subjects, 21.5%); pyrexia (60 subjects, 20.8%); and stomatitis (58 subjects, 20.1%). Grade ≥3 adverse events with an incidence of ≥5% were anaemia (60 subjects, 20.8%); neutrophil count decreased (53 subjects, 18.3%); white blood cell count decreased (37 subjects, 12.8%); platelet count decreased (33 subjects, 11.4%); and hypokalaemia (18 subjects, 6.2%). Serious adverse events with an incidence of ≥2% were pneumonitis (10 subjects, 3.5%); platelet count decreased (9 subjects, 3.1%); decreased appetite (8 subjects, 2.8%); anaemia, febrile neutropenia, and respiratory failure (6 subjects each, 2.1%). Adverse events leading to treatment discontinuation with an incidence of ≥2% were pneumonitis (22 subjects, 7.6%) and interstitial lung disease (11 subjects, 3.8%). Adverse events leading to dose interruption with an incidence of ≥2% were neutrophil count decreased (38 subjects, 13.1%); anaemia (20 subjects, 6.9%); platelet count decreased (11 subjects, 3.8%); decreased appetite and nausea (10

subjects each, 3.5%); pneumonitis (9 subjects, 3.1%); white blood cell count decreased (8 subjects, 2.8%); malaise and pyrexia (7 subjects each, 2.4%); nasopharyngitis, upper respiratory tract infection, and fatigue (6 subjects each, 2.1%). Adverse events leading to dose reduction with an incidence of ≥2% were decreased appetite (15 subjects, 5.2%); platelet count decreased (14 subjects, 4.8%); nausea (11 subjects, 3.8%); fatigue (10 subjects, 3.5%); malaise (9 subjects, 3.1%); anaemia (8 subjects, 2.8%); and neutrophil count decreased (6 subjects, 2.1%). No adverse events led to death with an incidence of ≥2%.

PMDA's discussion:

The adverse events, serious adverse events, and Grade ≥3 adverse events that occurred at a high incidence in Studies U201 and J101 are likely to occur when trastuzumab deruxtecan is used clinically; therefore, patients should be monitored closely for these events while being aware of the association with trastuzumab deruxtecan. Most of the adverse events were still manageable by dose interruption or reduction of trastuzumab deruxtecan. On the basis of the above findings, PMDA concluded that patients should be able to tolerate trastuzumab deruxtecan provided that appropriate steps including control and monitoring of adverse events and dose interruption/reduction are taken 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 trastuzumab deruxtecan between Japanese and non-Japanese populations based on the safety data from Studies U201 and J101:

Table 35 summarizes the safety data in Japanese and non-Japanese patients with unresectable or recurrent HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 35. Summary of safety data (patients with unresectable or recurrent HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 | | J101 | |
| | Japanese patients n = 30 | Non-Japanese patients n = 154 | Japanese patients n = 21 | Non-Japanese patients n = 29 |
| All adverse events | 30 (100) | 153 (99.4) | 21 (100) | 29 (100) |
| Grade ≥3 adverse events | 16 (53.3) | 78 (50.6) | 10 (47.6) | 13 (44.8) |
| Adverse events leading to death | 0 | 9 (5.8) | 1 (4.8) | 2 (6.9) |
| Serious adverse events | 4 (13.3) | 32 (20.8) | 4 (19.0) | 7 (24.1) |
| Adverse events leading to treatment discontinuation | 6 (20.0) | 9 (5.8) | 3 (14.3) | 4 (13.8) |
| Adverse events leading to dose interruption | 15 (50.0) | 42 (27.3) | 13 (61.9) | 8 (27.6) |
| Adverse events leading to dose reduction | 6 (20.0) | 31 (20.1) | 1 (4.8) | 4 (13.8) |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, adverse events of any grade with an incidence higher in Japanese patients than in non-Japanese patients by ≥20% were neutrophil count decreased[47] (22 subjects, 73.3% [Japanese]; 35 subjects, 22.7%

[47] Events classified as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) "neutrophil count decreased," and "neutropenia" were captured.

[non-Japanese]), anaemia[48)] (15 subjects, 50.0% [Japanese]; 33 subjects, 21.4% [non-Japanese]), white blood cell count decreased[49)] (22 subjects, 73.3% [Japanese]; 14 subjects, 9.1% [non-Japanese]), lymphocyte count decreased[50)] (9 subjects, 30.0% [Japanese]; 14 subjects, 9.1% [non-Japanese]), and ILD[51)] (9 subjects, 30.0% [Japanese]; 5 subjects, 3.2% [non-Japanese]). Grade ≥3 adverse events with an incidence higher in Japanese patients than in non-Japanese patients by ≥10% were neutrophil count decreased[47)] (10 subjects, 33.3% [Japanese]; 22 subjects, 14.3% [non-Japanese]) and white blood cell count decreased[49)] (5 subjects, 16.7% [Japanese]; 4 subjects, 2.6% [non-Japanese]). An adverse event leading to treatment discontinuation with an incidence higher in Japanese patients than in non-Japanese patients by ≥5% was ILD[51)] (5 subjects, 16.7% [Japanese]; 4 subjects, 2.6% [non-Japanese]). Adverse events leading to dose interruption with an incidence higher in Japanese patients than in non-Japanese patients by ≥5% were neutrophil count decreased[47)] (7 subjects, 23.3% [Japanese]; 18 subjects, 11.7% [non-Japanese]), white blood cell count decreased[49)] (2 subjects, 6.7% [Japanese]; 2 subjects, 1.3% [non-Japanese]), and ILD[51)] (5 subjects, 16.7% [Japanese]; 1 subject, 0.6% [non-Japanese]). No adverse events leading to death, serious adverse events, or adverse events leading to dose reduction occurred with an incidence higher in Japanese patients than in non-Japanese patients by ≥5%.

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, adverse events of any grade with an incidence higher in Japanese patients than in non-Japanese patients by ≥20% were anaemia[48)] (15 subjects, 71.4% [Japanese]; 9 subjects, 31.0% [non-Japanese]), decreased appetite (14 subjects, 66.7% [Japanese]; 9 subjects, 31.0% [non-Japanese]), platelet count decreased[52)] (9 subjects, 42.9% [Japanese]; 6 subjects, 20.7% [non-Japanese]), neutrophil count decreased[47)] (9 subjects, 42.9% [Japanese]; 3 subjects, 10.3% [non-Japanese]), pyrexia (8 subjects, 38.1% [Japanese]; 2 subjects, 6.9% [non-Japanese]), AST increased (7 subjects, 33.3% [Japanese]; 2 subjects, 6.9% [non-Japanese]), epistaxis (6 subjects, 28.6% [Japanese]; 2 subjects, 6.9% [non-Japanese]), malaise (6 subjects, 28.6% [Japanese]; 0 subjects, [non-Japanese]), and cystitis (5 subjects, 23.8% [Japanese]; 0 subjects [non-Japanese]). A Grade ≥3 adverse event with an incidence higher in Japanese patients than in non-Japanese patients by ≥10% was neutrophil count decreased[47)] (5 subjects, 23.8% [Japanese]; 1 subject, 3.4% [non-Japanese]). Adverse events leading to dose interruption with an incidence higher in Japanese patients than in non-Japanese patients by ≥5% were neutrophil count decreased[47)] (5 subjects, 23.8% [Japanese]; 0 subjects [non-Japanese]), nausea (2 subjects, 9.5% [Japanese]; 0 subjects [non-Japanese]), and pyrexia (2 subjects, 9.5% [Japanese]; 0 subjects [non-Japanese]). No adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation or dose reduction occurred with an incidence higher in Japanese patients than in non-Japanese patients by ≥5%.

48) Events classified as MedDRA PTs “anaemia,” “haemoglobin decreased,” and “red blood cell count decreased” were captured.
49) Events classified as MedDRA PTs “white blood cell count decreased” and “leukopenia” were captured.
50) Events classified as MedDRA PTs “lymphocyte count decreased” and “lymphopenia” were captured.
51) Events classified as MedDRA PTs “interstitial lung disease,” “pneumonitis,” “acute interstitial pneumonitis,” “organising pneumonia” were captured.
52) Events classified as MedDRA PTs “platelet count decreased” and “thrombocytopenia” were captured.

PMDA's discussion:

In Studies U201 and J101, only a limited number of Japanese patients were evaluated for safety after receiving trastuzumab deruxtecan 5.4 mg/kg, the proposed dosage regimen. While this precludes a strict comparison of differences between Japanese and non-Japanese populations, it was concluded that Japanese patients should also be able to tolerate trastuzumab deruxtecan by taking appropriate steps such as dose interruption, dose reduction, and treatment discontinuation of trastuzumab deruxtecan, based on the factors including those listed below.

- There were no clear trends towards increasing incidence of adverse events leading to death or serious adverse events in Japanese patients compared with non-Japanese patients.
- Although the incidence of ILD tended to be higher in Japanese patients than in non-Japanese patients, there were no clear trends towards increasing incidence of ILD leading to death or serious ILD in Japanese patients compared with non-Japanese patients.

On the basis of the safety results from Studies U201 and J101, PMDA reviewed adverse events primarily focusing on those that can be predicted from the mechanism of action of trastuzumab deruxtecan, and those that require caution in other HER2-targeted therapies such as trastuzumab, T-DM1, pertuzumab, and lapatinib.

### 7.R.3.3 ILD

The applicant's explanation about ILD associated with trastuzumab deruxtecan regarding (a) incidence; (b) difference in incidence between Japanese and non-Japanese patients; and (c) imaging features of ILD:

(a) Incidence of ILD

In the clinical studies of trastuzumab deruxtecan, in order to comprehensively evaluate adverse events suspected of being cases of ILD, reported adverse events classified in any of the following were evaluated by the independent ILD adjudication committee[53)]: standardised MedDRA queries (SMQs) "interstitial lung disease (narrow and selected broad terms)," MedDRA PTs "respiratory failure," and "acute respiratory failure."

Adverse events classified in the above categories were summarized. Table 36 shows the incidence of ILD as assessed by the independent ILD adjudication committee in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101 (data cut-off on February 1, 2019 [J101], and March 21, 2019 [U201]).

53) The independent ILD adjudication committee was composed of thoracic tumor specialists, respiratory specialists, and radiologists from Japan and the US. The committee reviewed and adjudicated suspected cases of ILD. When a case was diagnosed as ILD by the committee, the onset date, severity, causal relationship to trastuzumab deruxtecan, and causal relationship to death were adjudicated independent of the investigator.

**Table 36. Incidence of ILD (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| ILD | 16 (8.7) | 5 (2.7) | 8 (16.0) | 2 (4.0) |
| Pneumonitis | 7 (3.8) | 1 (0.5) | 3 (6.0) | 1 (2.0) |
| Interstitial lung disease | 5 (2.7) | 0 | 3 (6.0) | 0 |
| Acute respiratory failure | 1 (0.5) | 1 (0.5) | 0 | 0 |
| Respiratory failure | 1 (0.5) | 1 (0.5) | 2 (4.0) | 2 (4.0) |
| Alveolitis | 1 (0.5) | 0 | 0 | 0 |
| Lymphangitis* | 1 (0.5) | 1 (0.5) | 0 | 0 |
| Pneumonia | 1 (0.5) | 1 (0.5) | 0 | 0 |
| Organising pneumonia | 0 | 0 | 2 (4.0) | 0 |
| Lung infiltration | 0 | 0 | 1 (2.0) | 0 |

*, The event was initially reported as pneumonitis by the investigator, but subsequently changed to lymphangitis.

Of the patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, ILD led to death in 5 of 184 subjects (2.7%; pneumonitis [1 subject], acute respiratory failure [1 subject], respiratory failure [1 subject], lymphangitis [1 subject], and pneumonia [1 subject]), and a causal relationship to trastuzumab deruxtecan could not be ruled out for events in 4 of 184 subjects (2.2%; pneumonitis [1 subject], acute respiratory failure [1 subject], respiratory failure [1 subject], and lymphangitis [1 subject]). Serious ILD occurred in 5 of 184 subjects (2.7%; pneumonitis [1 subject], acute respiratory failure [1 subject], respiratory failure [1 subject], lymphangitis [1 subject], and pneumonia [1 subject]), and a causal relationship to trastuzumab deruxtecan could not be ruled out for events in 4 of 184 subjects (2.2%; pneumonitis [1 subject], acute respiratory failure [1 subject], respiratory failure [1 subject], and lymphangitis [1 subject]). ILD led to treatment discontinuation in 11 of 184 subjects (6.0%; pneumonitis [7 subjects], interstitial lung disease [2 subjects], alveolitis [1 subject], and pneumonia [1 subject]). ILD led to dose interruption in 4 of 184 subjects (2.2%; interstitial lung disease [3 subjects] and pneumonitis [1 subject]), and dose reduction in 2 of 184 subjects (1.1%; pneumonitis [1 subject] and interstitial lung disease [1 subject]).

Of the patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, ILD led to death in 2 of 50 subjects (4.0%; respiratory failure [2 subjects]), and a causal relationship to trastuzumab deruxtecan could not be ruled out for both events. Serious ILD occurred in 4 of 50 subjects (8.0%; pneumonitis [3 subjects] and respiratory failure [2 subjects], including duplicate data), and a causal relationship to trastuzumab deruxtecan could not be ruled out for these events. ILD led to treatment discontinuation in 5 of 50 subjects (10.0%; pneumonitis [3 subjects] and interstitial lung disease [2 subjects]). While ILD led to dose interruption in 2 of 50 subjects (4.0%; interstitial lung disease [1 subject] and organising pneumonia [1 subject]), no ILD events led to dose reduction.

Median time to first onset of ILD as determined by the independent ILD adjudication committee was 126.0 days (range, 42-378) in Study U201 and 214.5 days (range, 36-337) in Study J101.

Table 37 lists the details of patients who developed serious ILD associated with trastuzumab deruxtecan in all the ongoing and past clinical studies of trastuzumab deruxtecan (data cut-off on June 8, 2019).

**Table 37. List of patients who developed serious ILD (causally related to trastuzumab deruxtecan[*2])**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | Japanese/ non-Japanese | Primary disease | PT (MedDRA ver.20.1) | Grade[*2] | Onset[*1] (days) | Onset[*2] (days) | Duration[*1] (days) | Duration[*2] (days) | Trastuzumab deruxtecan treatment | Outcome[*1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5.4 | A104 | 69 | F | Japanese | Cervix carcinoma | Pneumonitis | 2 | 86 | Same as left | Un-known | Un-known | Dis-continued | Resolv-ing |
| | J101 | 72 | F | Japanese | Breast cancer | Pneumonitis | 2 | 253 | 247 | 182 | 188 | Dis-continued | Resolved |
| | | 66 | F | non-Japanese | Breast cancer | Respiratory failure | 5 | 182 | 40 | Un-known | Un-known | Not applicable | Death |
| | | 62 | F | non-Japanese | Breast cancer | Pneumonitis | 2 | 176 | 167 | 5 | 14 | Dis-continued | Resolved |
| | | 58 | F | non-Japanese | Breast cancer | Respiratory failure | 5 | 290 | 168 | 6 | 129 | Not applicable | Death |
| | U201 | 57 | F | non-Japanese | Breast cancer | Pneumonitis | 1 | 295 | 211 | Un-known | Un-known | Interrupted | Not resolved |
| | | 33 | F | non-Japanese | Breast cancer | Respiratory failure | 5 | 137 | 86 | Un-known | Un-known | Not applicable | Death |
| | | 65 | F | non-Japanese | Breast cancer | Interstitial lung disease | 3 | 246 | 134 | Un-known | Un-known | Dis-continued | Not resolved |
| | | 45 | F | non-Japanese | Breast cancer | Acute respiratory failure | 5 | 83 | Same as left | Un-known | Un-known | Not applicable | Death |
| | | 63 | F | non-Japanese | Breast cancer | Pneumonitis | 2 | 295 | Same as left | 14 | 14 | Dis-continued | Resolved |
| | | 64 | F | non-Japanese | Breast cancer | Pneumonitis | 5 | 148 | 124 | Un-known | Un-known | Not applicable | Death |
| | | 62 | F | non-Japanese | Breast cancer | Lymphangitis | 5 | 63 | 39 | 10 | 34 | Unknown | Death |
| | U301 | 70 | F | Japanese | Breast cancer | Interstitial lung disease | 3 | Un-known | Un-known | Un-known | Un-known | Dis-continued | Not resolved |
| | | 48 | F | non-Japanese | Breast cancer | Pneumonitis | 5 | 71 | Same as left | 13 | 13 | Dis-continued | Death |
| 6.4 | A103 | 62 | F | non-Japanese | Breast cancer | Interstitial lung disease | 5 | 151 | 83 | Un-known | Un-known | Not applicable | Death |
| | J101 | 55 | F | Japanese | Breast cancer | Pneumonitis | 2 | 175 | 127 | 135 | 183 | Dis-continued | Resolv-ing |
| | | 64 | F | Japanese | Breast cancer | Interstitial lung disease | 2 | 141 | Same as left | 267 | 267 | Dis-continued | Resolved |
| | | 63 | F | Japanese | Breast cancer | Interstitial lung disease | 5 | 371 | 365 | Un-known | Un-known | Not applicable | Death |
| | | 58 | F | Japanese | Breast cancer | Interstitial lung disease | 3 | 85 | 84 | 39 | 40 | Dis-continued | Resolved |
| | | 53 | M | Japanese | Salivary gland cancer | Interstitial lung disease | 3 | 325 | 258 | Un-known | Un-known | Dis-continued | Not resolved |
| | | 64 | F | Japanese | Breast cancer | Pneumonitis | 5 | 129 | Same as left | Un-known | Un-known | Not applicable | Death |
| | | 49 | F | Japanese | Breast cancer | Pneumonitis | 5 | 440 | 435 | Un-known | Un-known | Not applicable | Death |
| | | 51 | F | non-Japanese | Breast cancer | Pneumonitis | 5 | 194 | 83 | Un-known | Un-known | Not applicable | Death |
| | | 52 | F | non-Japanese | Breast cancer | Respiratory failure | 5 | 46 | Same as left | Un-known | Un-known | Dis-continued | Not resolved |
| | | 48 | M | non-Japanese | Non-small cell lung cancer | Respiratory failure | 5 | 27 | −15 | Un-known | Un-known | Not applicable | Death |
| | | 83 | F | non-Japanese | Non-small cell lung cancer | Pneumonitis | 3 | 282 | 246 | Un-known | Un-known | Dis-continued | Not resolved |

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | Japanese/ non-Japanese | Primary disease | PT (MedDRA ver.20.1) | Grade*2 | Onset*1 (days) | Onset*2 (days) | Duration*1 (days) | Duration*2 (days) | Trastuzumab deruxtecan treatment | Outcome*1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | J102 | 70 | F | Japanese | Breast cancer | Pneumonitis | 3 | 316 | 260 | 36 | 92 | Dis-continued | Resolv-ing |
| | | 65 | F | Japanese | Breast cancer | Interstitial lung disease | 3 | 225 | 169 | 8 | 64 | Dis-continued | Resolv-ing |
| | J203 | 62 | F | non-Japanese | Colorectal cancer | Pneumonitis | 5 | 119 | 120 | 8 | 7 | Dis-continued | Death |
| | | 60 | M | non-Japanese | Colorectal cancer | Interstitial lung disease | 5 | 22 | Same as left | Un-known | Un-known | Dis-continued | Death |
| | U201 | 67 | F | Japanese | Breast cancer | Interstitial lung disease | 2 | 65 | Same as left | 147 | 147 | Dis-continued | Resolved |
| | U204 | 56 | M | Japanese | Lung cancer | Pneumonitis | 2 | 86 | Same as left | Un-known | Un-known | Dis-continued | Not resolved |
| 7.4 | U201 | 65 | F | Japanese | Breast cancer | Interstitial lung disease | 3 | 179 | 168 | Un-known | Un-known | Not applicable | Not resolved |
| | | 67 | F | non-Japanese | Breast cancer | Pneumonitis | 5 | 266 | 253 | Un-known | Un-known | Dis-continued | Death |
| 8.0 | J101 | 74 | F | non-Japanese | Breast cancer | Pneumonitis | 5 | 422 | 380 | Un-known | Un-known | Not applicable | Death |
| Unknown | J202 | 68 | M | Japanese | Gastric cancer | Pneumonitis | 2 | 164 | Same as left | 21 | 21 | Continued | Resolv-ing |
| | | 73 | M | Japanese | Gastric cancer | Interstitial lung disease | 3 | 124 | 85 | 57 | 96 | Dis-continued | Resolv-ing |
| | | 80 | F | Japanese | Gastric cancer | Pneumonitis | 4 | 36 | Same as left | Un-known | Un-known | Continued | Not resolved |

*1, Assessed by the investigator; *2, assessed by the independent ILD adjudication committee

The incidence of ILD as adjudicated by the independent ILD adjudication committee in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101 up to the most recent cut-off date (August 1, 2019) were as follows: ILD of any grade in 35 of 234 subjects (15.0%), Grade ≥3 ILD in 8 of 234 subjects (3.4%), ILD leading to death in 7 of 234 subjects (3.0%), and serious ILD in 13 of 234 subjects (5.6%).

(b) Difference in the incidence of ILD between Japanese and non-Japanese patients

Table 38 shows the incidence of ILD in Japanese and non-Japanese patients in the 5 clinical studies included in the data submitted for the present application (data cut-off dates: February 1, 2019 [J101]; September 14, 2018 [A103]; September 26, 2018 [A104]; December 5, 2018 [J102]; and March 21, 2019 [U201]).

**Table 38. Incidence of ILD in Japanese and non-Japanese patients (causally related to trastuzumab deruxtecan)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | Japanese patients n = 316 | | Non-Japanese patients n = 329 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| ILD | 51 (16.1) | 5 (1.6) | 21 (6.4) | 11 (3.3) |
| Pneumonitis | 24 (7.6) | 2 (0.6) | 14 (4.3) | 6 (1.8) |
| Interstitial lung disease | 24 (7.6) | 3 (0.9) | 0 | 0 |
| Organising pneumonia | 4 (1.3) | 0 | 2 (0.6) | 0 |
| Radiation pneumonitis | 1 (0.3) | 0 | 0 | 0 |
| Respiratory failure | 0 | 0 | 5 (1.5) | 5 (1.5) |
| Alveolitis | 0 | 0 | 1 (0.3) | 0 |
| Lung infiltration | 0 | 0 | 1 (0.3) | 0 |
| Acute respiratory failure | 0 | 0 | 1 (0.3) | 1 (0.3) |
| Lymphangitis* | 0 | 0 | 1 (0.3) | 1 (0.3) |

*, The event was initially reported as pneumonitis by the investigator, but subsequently changed to lymphangitis.

Among Japanese patients, serious ILD events occurred in 10 of 316 subjects (3.2%; pneumonitis [5 subjects] and interstitial lung disease [5 subjects]). ILD led to death in 2 of 316 subjects (0.6%; pneumonitis [1 subject] and interstitial lung disease [1 subject]), and both of the subjects had received trastuzumab deruxtecan 6.4 mg/kg. Of the Japanese patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg, ILD events of any grade occurred in 10 of 51 subjects (19.6%; interstitial lung disease [8 subjects] and pneumonitis [3 subjects], including duplicate data), and serious ILD occurred in 1 of 51 subjects (2.0%; pneumonitis). No ILD events led to death.

On the basis of the above results, taking into account that majority of the events of ILD that occurred in Japanese patients were Grade ≤2 in severity, ILD in patients with HER2-positive breast cancer following administration of trastuzumab deruxtecan 5.4 mg/kg is considered to be manageable.

(c) Imaging features of ILD

The imaging features[54)] of ILD that occurred following administration of trastuzumab deruxtecan were examined based on the data from 72 patients from 5 clinical studies included in the data submitted for the present application, and the following patterns of imaging features were observed: the diffuse alveolar damage pattern (DAD pattern), 16 of 72 subjects (22.2%); organising pneumonia-like pattern (OP-like pattern), 50 of 72 subjects (69.4%); hypersensitivity pneumonia-like pattern (HP-like pattern), 5 of 72 subjects (6.9%); and non-specific interstitial pneumonia-like pattern (NSIP-like pattern), 1 of 72 subjects (1.4%). By severity, Grades 1 and 2 ILD events in 48 of 56 subjects (85.7%) were classified as the OP-like pattern; Grades 3 to 5 ILD events in 14 of 16 subjects (87.5%) were classified as the DAD pattern. Of the ILD events assessed as the OP-like pattern, the outcome of ILD in 31 of 50 subjects (62.0%) was reported as unresolved, including 1 death. On the basis of the above findings, while the imaging features of ILD events following administration of trastuzumab deruxtecan seem to be correlated with the severity to some degree, it is difficult to come to a conclusion regarding its relationship with the outcome.

54) The image-based characteristics were classified based on the Japanese Respiratory Society Guidelines for the Management of Drug-induced Lung Disease 2018.

In addition to the above, the onset date of ILD as determined by the independent ILD adjudication committee differed[55] from that as determined by the investigator in 27 of 72 subjects (37.5%) with the median difference in onset date being 24 days (range, 1-210). Similarly, in Japanese patients, discrepancy in the onset date of ILD was observed in 18 of 51 subjects (35.3%) with the median difference in onset date being 34.5 days (range, 1-210). Examination results of onset dates based on ILD imaging features were as follows: the onset date as determined by the independent ILD adjudication committee differed from that as determined by the investigator in 8 of 16 subjects (50.0%) in the DAD pattern with the median difference in onset date being 24 days (range, 6-142); 16 of 50 subjects (32.0%) in the OP-like pattern with the median difference in onset date being 24.5 days (range, 1-210); 2 of 5 subjects (40.0%) in the HP-like pattern with the median difference in onset date being 20.5 days (range, 1-40); and 1 of 1 subject (100%) in the NSIP-like pattern with the difference being 21 days. The finding indicated a discrepancy in the onset date of ILD between the independent ILD adjudication committee and the investigator regardless of imaging features.

Given the discrepancies in the date of ILD diagnosis following administration of trastuzumab deruxtecan, it is considered necessary to take steps including regular chest computed tomography (CT) scans and prompt interpretation of chest CT scans by specialists in order to diagnose ILD associated with trastuzumab deruxtecan in an appropriate manner.

PMDA asked the applicant to explain the mechanism of onset and risk factors of ILD associated with trastuzumab deruxtecan.

The applicant's response:
The mechanism of onset of ILD associated with trastuzumab deruxtecan was examined based on the toxicity study in cynomolgus monkeys, in which, as with humans, HER2 can be expressed in bronchial epithelial cells. The results suggest that the expression sites of pulmonary toxicity did not coincide with the sites of anti-HER2 antibody binding sites in cynomolgus monkeys, and that MAAA-1181a was not distributed in bronchial epithelial cells in cynomolgus monkeys [see Section 5.R.1]. Based on the findings including these results, the mechanism of onset of ILD by trastuzumab deruxtecan is unclear.

The risk factors[56] for the onset of ILD associated with trastuzumab deruxtecan were analyzed using pooled data (n = 645) from 5 clinical studies included in the data submitted for the present application. The analysis identified the following risk factors: country being Japan, and the number of prior regimens being ≥10,[57] with the odds ratio [95% CI] being 3.1 [1.8, 5.3] and 2.4 [1.4, 4.3], respectively.

---

55) When an onset date of an event determined by the independent ILD adjudication committee was earlier than the onset date determined by the investigator by ≥1 day, it was counted as a case of discrepancy in determining the onset date.

56) An analysis was performed using a logistic regression model to evaluate 12 potential risk factors: age (≥65 years or <65 years), sex, race (Asian, white, or other), country (Japan or non-Japan), region (Asia or non-Asia), tumor type (breast cancer, gastric cancer, or other), lung malignancy (presence or absence), prior thoracic radiotherapy (presence or absence), lung comorbidities (presence or absence), number of prior chemotherapy regimens (≥10 or <10), time since diagnosis of primary disease (≥62.8 months or <62.8 months), and initial dose of trastuzumab deruxtecan (≥6.4 mg/kg or 5.4 mg/kg).

57) 115 of 645 subjects (17.8%) included in the analysis had ≥10 prior chemotherapy regimens.

PMDA asked the applicant to explain about the treatment of ILD that emerges following administration of trastuzumab deruxtecan.

The applicant's response:
In Studies U201 and J101, corticosteroid was recommended for the treatment of ILD based on the treatment guidelines (*Respir Investig*. 2013;51:260-77 and Japanese Respiratory Society Guidelines for the Management of Drug-induced Lung Disease 2018 [in Japanese]); however, the dosage regimen of corticosteroids and criteria for initiation of corticosteroid treatment were not specified in the protocol. Consequently, of the 39 corticosteroid-treated patients from the 5 clinical studies included in the data submitted for the present application who had ILD following trastuzumab deruxtecan, the outcome was reported as follows: unresolved in 15 subjects (38.5%) and death in 5 subjects (12.8%), indicating that more than half the patients have not recovered. In one of the death cases, a long period elapsed from the time of ILD onset to the initiation of corticosteroid treatment.

On the basis of the above, since early initiation of suitable treatment such as corticosteroids is critical for ILD, specific timing of intervention with corticosteroids should be given in the package insert and caution should be advised to ensure that treatment for ILD following trastuzumab deruxtecan can be initiated as soon as possible.

PMDA's discussion:
When using trastuzumab deruxtecan, the patient should be monitored closely for development of ILD, taking into account the findings associated with trastuzumab deruxtecan including the following: (a) ILD leading to death and serious ILD for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred; (b) a discrepancy has been identified in the date of ILD diagnosis between the independent ILD adjudication committee and the investigator, suggesting difficulties in image-based diagnosis by physicians other than respiratory specialists or radiologists; and (c) more than half the patients who received corticosteroid treatment have not recovered. Furthermore, taking into consideration that the incidence of ILD associated with trastuzumab deruxtecan was higher in Japanese patients than in non-Japanese patients [see Section 7.R.3.2], when administering trastuzumab deruxtecan to a Japanese patient, the patient should be monitored for ILD with particular caution.

Therefore, it was concluded that using information materials such as the package insert, the occurrence of ILD in the clinical studies, risk factors, imaging features, and other information should be provided, and healthcare professionals should be advised appropriately to exercise caution so that the following actions can be taken:

- Before starting treatment with trastuzumab deruxtecan, eligible patients should be carefully selected after verifying current or history of ILD, and other factors.
- During treatment with trastuzumab deruxtecan, patients should be monitored continuously for clinical symptoms, arterial blood oxygen saturation ($SpO_2$), and imaging examinations such as CT

should be performed. Diagnosis based on the CT images obtained should be performed by specialists.

- When ILD is suspected based on clinical symptoms or other factors, appropriate actions such as discontinuation of trastuzumab deruxtecan or corticosteroid treatment should be taken in cooperation with respiratory specialists.

In addition to the above, taking into account the findings including a higher incidence of ILD associated with trastuzumab deruxtecan in Japanese patients than in non-Japanese patients, information regarding risk factors for development of ILD in Japanese patients is extremely important for the purposes of predicting safety and appropriate selection of eligible patients; therefore, risk factors for ILD should be examined in the post-marketing setting of trastuzumab deruxtecan.

### 7.R.3.4 Myelosuppression

The applicant's explanation about myelosuppression associated with trastuzumab deruxtecan:
To evaluate myelosuppression, events classified as MedDRA PTs "haemoglobin decreased," "red blood cell count decreased," "anaemia," "neutrophil count decreased," "neutropenia," "platelet count decreased," "thrombocytopenia," "white blood cell count decreased," "leukopenia," "lymphocyte count decreased," "lymphopenia," "pancytopenia," and "febrile neutropenia" were captured.

Table 39 shows the incidence of myelosuppression in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 39. Myelosuppression with an incidence of ≥1% in at least one of the studies (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Myelosuppression | 90 (48.9) | 43 (23.4) | 31 (62.0) | 11 (22.0) |
| Anaemia | 47 (25.5) | 12 (6.5) | 23 (46.0) | 5 (10.0) |
| Neutrophil count decreased | 37 (20.1) | 18 (9.8) | 12 (24.0) | 6 (12.0) |
| White blood cell count decreased | 32 (17.4) | 8 (4.3) | 9 (18.0) | 1 (2.0) |
| Platelet count decreased | 24 (13.0) | 5 (2.7) | 15 (30.0) | 2 (4.0) |
| Neutropenia | 21 (11.4) | 14 (7.6) | 0 | 0 |
| Lymphocyte count decreased | 14 (7.6) | 6 (3.3) | 0 | 0 |
| Lymphopenia | 10 (5.4) | 4 (2.2) | 0 | 0 |
| Thrombocytopenia | 8 (4.3) | 1 (0.5) | 0 | 0 |
| Leukopenia | 4 (2.2) | 1 (0.5) | 0 | 0 |
| Febrile neutropenia | 3 (1.6) | 3 (1.6) | 1 (2.0) | 1 (2.0) |
| Haemoglobin decreased | 2 (1.1) | 0 | 0 | 0 |
| Red blood cell count decreased | 1 (0.5) | 0 | 1 (2.0) | 0 |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, serious myelosuppression occurred in 1 of 184 subjects (0.5%; anaemia), and a causal relationship to trastuzumab deruxtecan was denied for this event. Myelosuppression led to treatment discontinuation in 1 of 184 subjects (0.5%; thrombocytopenia). Myelosuppression led to dose interruption in 29 of 184

subjects (15.8%; neutrophil count decreased [14 subjects], neutropenia [11 subjects], anaemia [7 subjects], platelet count decreased [4 subjects], white blood cell count decreased [4 subjects], and thrombocytopenia [1 subject], including duplicate data), and dose reduction in 8 of 184 subjects (4.3%; neutrophil count decreased [2 subjects], neutropenia [2 subjects], platelet count decreased [2 subjects], anaemia [1 subject], and febrile neutropenia [1 subject]). No events of myelosuppression led to death.

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, serious myelosuppression occurred in 1 of 50 subjects (2.0%; febrile neutropenia), and a causal relationship to trastuzumab deruxtecan could not be ruled out for this event. Myelosuppression led to dose interruption in 8 of 50 subjects (16.0%; neutrophil count decreased [5 subjects], platelet count decreased [2 subjects], anaemia [1 subject], white blood cell count decreased [1 subject], and febrile neutropenia [1 subject], including duplicate data), and dose reduction in 1 of 50 subjects (2.0%; neutrophil count decreased). No events of myelosuppression led to death, or treatment discontinuation.

Table 40 shows details of patients who developed serious myelosuppression associated with trastuzumab deruxtecan in Studies U201 and J101.

**Table 40. List of patients who developed serious myelosuppression (causally related to trastuzumab deruxtecan)**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | PT (MedDRA ver.20.1) | Grade | Onset (days) | Duration (days) | Trastuzumab deruxtecan treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 5.4 | J101 | 58 | F | Anaemia | 2 | 45 | 1 | Continued | Not resolved |
| | | | | Anaemia | 3 | 46 | 12 | Continued | Resolved |
| | | 66 | F | Febrile neutropenia | 3 | 81 | 12 | Interrupted | Resolved |
| 6.4 | U201 | 78 | F | White blood cell count decreased | 4 | 20 | 4 | Continued | Resolved |
| | | 54 | F | Thrombocytopenia | 4 | 8 | Continuous | Discontinued | Not resolved |
| | J101 | 54 | F | Anaemia | 3 | 228 | 11 | Reduced | Resolved |
| | | 75 | F | Anaemia | 3 | 133 | Unknown | Interrupted | Not resolved |
| | | 54 | F | Platelet count decreased | 3 | 228 | Unknown | Reduced | Not resolved |
| | | 48 | F | Platelet count decreased | 3 | 139 | 10 | Continued | Resolved |
| | | 68 | F | Platelet count decreased | 4 | 82 | 25 | Continued | Resolving |
| | | 73 | M | Platelet count decreased | 4 | 10 | Unknown | Reduced | Not resolved |
| | | 67 | F | Platelet count decreased | 3 | 11 | 13 | Continued | Resolved |
| | | 67 | F | Platelet count decreased | 4 | 332 | Unknown | Continued | Not resolved |
| | | 45 | F | Platelet count decreased | 4 | 9 | 7 | Continued | Resolved |
| | | 47 | F | Platelet count decreased | 4 | 162 | Unknown | Discontinued | Not resolved |
| | | 63 | M | Febrile neutropenia | 3 | 13 | 9 | Reduced | Resolved |
| | | 58 | M | Febrile neutropenia | 5 | 61 | 4 | Not applicable | Death |
| | | 67 | F | Febrile neutropenia | 3 | 11 | 13 | Continued | Resolved |
| 7.4 | U201 | 46 | F | Febrile neutropenia | 4 | 8 | 6 | Reduced | Resolved |

Median time to first onset of myelosuppression was 22.0 days (range, 1-210) in Study U201 and 29.0 days (range, 2-324) in Study J101.

PMDA's discussion:

In the clinical studies included in the submitted data, myelosuppression including Grade ≥3 events associated with trastuzumab deruxtecan occurred at a certain incidence, and a case of fatal myelosuppression for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred. Considering these findings, the patient should be closely monitored for development of myelosuppression when using trastuzumab deruxtecan. Therefore, it was concluded that healthcare professionals should be advised appropriately to exercise caution by providing information on myelosuppression events that occurred in the clinical studies as well as providing advice on their management using information materials such as the package insert.

### 7.R.3.5 IRRs

The applicant's explanation about IRR associated with trastuzumab deruxtecan:

To evaluate IRRs, events classified as the following MedDRA PTs that occurred within the same day of infusion of trastuzumab deruxtecan were captured: "infusion related reaction," "flushing," "anaphylactic reaction," "dyspnoea," "hypotension," "wheezing," "hypersensitivity," "bronchospasm," "pruritus," "angioedema," "urticaria," "skin exfoliation," "oedema," and "rash."

Table 41 shows the incidence of IRRs in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 41. Incidence of IRRs (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| IRR | 15 (8.2) | 0 | 2 (4.0) | 0 |
| Dyspnoea | 5 (2.7) | 0 | 1 (2.0) | 0 |
| Infusion related reaction | 4 (2.2) | 0 | 0 | 0 |
| Pruritus | 2 (1.1) | 0 | 0 | 0 |
| Hypersensitivity | 1 (0.5) | 0 | 0 | 0 |
| Flushing | 1 (0.5) | 0 | 0 | 0 |
| Hypotension | 1 (0.5) | 0 | 1 (2.0) | 0 |
| Bronchospasm | 1 (0.5) | 0 | 0 | 0 |
| Oedema | 1 (0.5) | 0 | 0 | 0 |

Of the events of IRR that occurred in Study U201, events identified by the applicant to be IRR[58)] occurred in 6 subjects (3.3%; infusion related reaction [4 subjects], hypersensitivity [1 subject], and flushing [1 subject]). Of the events identified by the applicant to be IRR, a serious event of IRR occurred in 1 subject (0.5%; hypersensitivity), for which a causal relationship to trastuzumab deruxtecan could not be ruled out. IRR led to treatment discontinuation in 1 subject (0.5%; infusion related reaction). All patients were able to continue or resume treatment with trastuzumab deruxtecan.

58) It was comprehensively determined based on the onset time, time to recovery, other potential causes, recurrence after resuming treatment, and other factors.

Of the events of IRR that occurred in Study J101, none of the events was identified by the applicant to be IRR.

In Study U201, the median time to first onset of the applicant-identified IRR event was 1 day (range, 1-178).

In Studies U201 and J101, no prophylactic treatment for IRR was specified.

In all the ongoing and past clinical studies of trastuzumab deruxtecan, a serious event of IRR associated with trastuzumab deruxtecan occurred in 1 patient with details shown in Table 42.

**Table 42. Details of the patient who developed a serious event of IRR**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | Primary disease | PT (MedDRA ver.20.1) | Grade | Onset (days) | Duration (days) | Trastuzumab deruxtecan treatment | Causal relation-ship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5.4 | U201 | 48 | F | Breast cancer | Hyper-sensitivity | 1 | 127 | 2 | Continued | Yes | Resolved |

PMDA's discussion:
In the clinical studies included in the submitted data, IRR associated with trastuzumab deruxtecan occurred at a certain incidence, and a serious adverse event of IRR for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred. Considering these findings, the patient should be closely monitored for development of IRR when using trastuzumab deruxtecan. Therefore, it was concluded that healthcare professionals should be advised appropriately to exercise caution by providing information on IRR that occurred in the clinical studies as well as providing advice on their management using information materials such as the package insert.

### 7.R.3.6 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with trastuzumab deruxtecan:
To evaluate hepatic dysfunction, events classified as MedDRA SMQ "drug related hepatic disorders (narrow)" were captured.

Table 43 shows the incidence of hepatic dysfunction in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 43. Hepatic dysfunction events with an incidence of ≥1% in at least one of the studies (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Hepatic dysfunction | 45 (24.5) | 9 (4.9) | 15 (30.0) | 1 (2.0) |
| AST increased | 23 (12.5) | 2 (1.1) | 9 (18.0) | 0 |
| ALT increased | 17 (9.2) | 2 (1.1) | 7 (14.0) | 0 |
| Blood bilirubin increased | 11 (6.0) | 0 | 2 (4.0) | 0 |
| γ-GTP increased | 5 (2.7) | 1 (0.5) | 0 | 0 |
| Ascites | 3 (1.6) | 2 (1.1) | 2 (4.0) | 0 |
| Liver function test increased | 2 (1.1) | 0 | 0 | 0 |
| Hyperbilirubinaemia | 1 (0.5) | 0 | 1 (2.0) | 1 (2.0) |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, hepatic dysfunction led to death in 1 of 184 subjects (0.5%; acute hepatic failure), and a causal relationship to trastuzumab deruxtecan was denied for this event. Serious hepatic dysfunction occurred in 2 of 184 subjects (1.1%; ascites [1 subject] and acute hepatic failure [1 subject]), and a causal relationship to trastuzumab deruxtecan was denied for both events. Hepatic dysfunction led to dose interruption in 4 of 184 subjects (2.2%; blood bilirubin increased [2 subjects], ALT increased [1 subject], and γ-GTP increased [1 subject]), and dose reduction in 5 of 184 subjects (2.7%; blood bilirubin increased [4 subjects], AST increased [1 subject], and ALT increased [1 subject], including duplicate data). No events of hepatic dysfunction led to treatment discontinuation.

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, hepatic dysfunction led to dose interruption in 1 of 50 subjects (2.0%; blood bilirubin increased). No hepatic dysfunction events led to death, or serious hepatic dysfunction were reported. No hepatic dysfunction events led to treatment discontinuation or dose reduction.

Median time to first onset of hepatic dysfunction was 64.0 days (range, 4-211) in Study U201, and 40.0 days (range, 2-330) in Study J101.

Table 44 shows the details of patients who developed serious hepatic dysfunction associated with trastuzumab deruxtecan in Studies U201 and J101.

**Table 44. List of patients who developed serious hepatic dysfunction (causally related to trastuzumab deruxtecan)**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | PT (MedDRA ver.20.1) | Grade | Onset (days) | Duration (days) | Trastuzumab deruxtecan treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 5.4 | U201 | 61 | F | Liver disorder | 2 | 330 | 6 | Continued | Resolved |
| 6.4 | J101 | 58 | M | Hepatic function abnormal | 5 | 57 | 8 | Not applicable | Death |
| 8.0 | | 74 | F | Blood bilirubin increased | 2 | 422 | Continuous | Not applicable | Not resolved |
| 7.4 | U201 | 46 | F | ALT increased | 2 | 7 | 3 | Continued | Resolved |
| | | | | AST increased | 3 | 7 | 4 | Continued | Resolved |

In all the clinical studies included in the submitted data, 9 patients developed hepatic dysfunction based on the laboratory data that met the Hy's law criteria (defined in accordance with the *Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* U.S. Department of Health and Human Services, Food and Drug Administration. July 2009); however, a causal relationship to trastuzumab deruxtecan was denied for all events.

PMDA's discussion:
In the clinical studies included in the submitted data, events of hepatic dysfunction associated with trastuzumab deruxtecan have been reported, including serious adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out. Findings including the above suggest that the patient should be closely monitored for development of hepatic dysfunction when using trastuzumab deruxtecan. Therefore, it was concluded that healthcare professionals should be advised appropriately to exercise caution by providing information on hepatic dysfunction events that occurred in the clinical studies as well as providing advice on their management using information materials such as the package insert.

### 7.R.3.7 Cardiac disorders (excluding QT interval prolongation)

The applicant's explanation about cardiac disorders associated with trastuzumab deruxtecan:
To evaluate cardiac disorders, events classified as the following MedDRA PTs were captured: "acute left ventricular failure," "acute right ventricular failure," "cardiac failure," "cardiac failure acute," "cardiac failure chronic," "cardiac failure congestive," "chronic left ventricular failure," "chronic right ventricular failure," "ejection fraction decreased," "left ventricular failure," "right ventricular failure," and "ventricular failure."

Table 45 shows the incidence of cardiac disorders in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 45. Incidence of cardiac disorders (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Cardiac disorders | 4 (2.2) | 1 (0.5) | 0 | 0 |
| Ejection fraction decreased | 2 (1.1) | 1 (0.5) | 0 | 0 |
| Cardiac failure | 1 (0.5) | 0 | 0 | 0 |
| Cardiac failure congestive | 1 (0.5) | 0 | 0 | 0 |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, a serious event of cardiac disorder occurred in 1 of 184 subjects (0.5%; cardiac failure congestive), for which a causal relationship to trastuzumab deruxtecan could not be ruled out. Cardiac disorders led to treatment discontinuation in 1 of 184 subjects (0.5%; cardiac failure congestive), and dose interruption

in 2 of 184 subjects (1.1%; ejection fraction decreased [2]). No cardiac disorders led to death or dose reduction.

Median time to first onset of cardiac disorders was 123.0 days (range, 1-187) in Study U201.

In all the ongoing and past clinical studies of trastuzumab deruxtecan, a serious event of cardiac disorder associated with trastuzumab deruxtecan occurred in 1 patient with details shown in Table 46.

**Table 46. Details of the patient who developed a serious event of cardiac disorder**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | Primary disease | PT (MedDRA ver.20.1) | Grade | Onset (days) | Duration (days) | Trastuzumab deruxtecan treatment | Causal relation-ship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5.4 | U201 | 67 | F | Breast cancer | Cardiac failure congestive | 2 | 187 | 44 | Discontinued | Yes | Resolved |

PMDA's discussion:
In the clinical studies included in the submitted data, cardiac disorders associated with trastuzumab deruxtecan have been reported, and a serious event of cardiac disorder has occurred for which a causal relationship to trastuzumab deruxtecan could not be ruled out. In addition, cardiac disorders have already been identified as risks for conventional HER2-targeted drugs (e.g., trastuzumab and T-DM1). Considering these factors, the patient should be closely monitored for development of cardiac disorders when using trastuzumab deruxtecan. Therefore, it was concluded that healthcare professionals should be advised appropriately to exercise caution by providing information on cardiac disorders that occurred in the clinical studies as well as providing advice on their management using information materials such as the package insert.

### 7.R.3.8 Other events

The applicant's explanation about the incidence of the following events that are likely to occur associated with trastuzumab deruxtecan based on the occurrence of adverse events associated with similar HER2-targeted drugs already in the market: (a) gastrointestinal disorders, (b) QT interval prolongation, and (c) tumour lysis syndrome:

(a) Gastrointestinal disorders

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

Table 47 shows the incidence of gastrointestinal disorders in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 47. Gastrointestinal disorder events with an incidence of ≥3% in at least one of the studies (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Gastrointestinal disorders | 170 (92.4) | 27 (14.7) | 48 (96.0) | 5 (10.0) |
| Nausea | 142 (77.2) | 14 (7.6) | 43 (86.0) | 2 (4.0) |
| Vomiting | 83 (45.1) | 7 (3.8) | 28 (56.0) | 2 (4.0) |
| Constipation | 63 (34.2) | 1 (0.5) | 18 (36.0) | 1 (2.0) |
| Decreased appetite | 53 (28.8) | 3 (1.6) | 23 (46.0) | 0 |
| Diarrhoea | 49 (26.6) | 3 (1.6) | 18 (36.0) | 1 (2.0) |
| Stomatitis | 23 (12.5) | 2 (1.1) | 7 (14.0) | 0 |
| Dyspepsia | 22 (12.0) | 0 | 7 (14.0) | 0 |
| Abdominal pain | 21 (11.4) | 2 (1.1) | 7 (14.0) | 0 |
| Gastrooesophageal reflux disease | 15 (8.2) | 0 | 3 (6.0) | 0 |
| Abdominal pain upper | 11 (6.0) | 0 | 2 (4.0) | 0 |
| Haemorrhoids | 9 (4.9) | 1 (0.5) | 0 | 0 |
| Dry mouth | 5 (2.7) | 0 | 2 (4.0) | 0 |
| Abdominal distension | 4 (2.2) | 0 | 3 (6.0) | 0 |
| Dysphagia | 4 (2.2) | 1 (0.5) | 2 (4.0) | 0 |
| Flatulence | 3 (1.6) | 0 | 2 (4.0) | 0 |
| Ascites | 3 (1.6) | 2 (1.1) | 2 (4.0) | 0 |
| Abdominal discomfort | 1 (0.5) | 0 | 4 (8.0) | 0 |
| Gingival bleeding | 1 (0.5) | 0 | 3 (6.0) | 0 |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, serious events of gastrointestinal disorders occurred in 12 of 184 subjects (6.5%; vomiting [4 subjects], nausea [3 subjects], intestinal obstruction [3 subjects], abdominal pain [2 subjects], dysphagia [1 subject], ascites [1 subject], and upper gastrointestinal haemorrhage [1 subject], including duplicate data), and among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for events in 7 of 184 subjects (3.8%; vomiting [4 subjects], nausea [3 subjects], and dysphagia [1 subject], including duplicate data). Gastrointestinal disorders led to dose interruption in 6 of 184 subjects (3.3%; nausea [3 subjects], vomiting [2 subjects], diarrhoea [2 subjects], and periodontal disease [1 subject], including duplicate data), and dose reduction in 12 of 184 subjects (6.5%; nausea [5 subjects], vomiting [3 subjects], decreased appetite [2 subjects], diarrhoea [1 subject], stomatitis [1 subject], and haemorrhoids [1 subject], including duplicate data). No events of gastrointestinal disorders led to death or treatment discontinuation.

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, a serious event of gastrointestinal disorder occurred in 1 of 50 subjects (2.0%; diarrhoea haemorrhagic), and a causal relationship to trastuzumab deruxtecan could not be ruled out for this event. Gastrointestinal disorders led to dose interruption in 3 of 50 subjects (6.0%; nausea [2 subjects] and vomiting [1 subject]), and dose reduction in 2 of 50 subjects (4.0%; nausea [2 subjects]). No events of gastrointestinal disorders led to death or treatment discontinuation.

Median time to first onset of gastrointestinal disorders was 2.0 days (range, 1-151) in Study U201, and 2.0 days (range, 1-576) in Study J101.

(b) QT interval prolongation

To evaluate QT interval prolongation, events classified as the following MedDRA PTs were captured: "electrocardiogram QT prolonged," "electrocardiogram QT interval abnormal," "torsade de pointes," "sudden cardiac death," "sudden death," "syncope," "ventricular arrhythmia," "ventricular fibrillation," "ventricular flutter," "ventricular tachyarrhythmia," "ventricular tachycardia," and "seizure."

Table 48 shows the incidence of QT interval prolongation events in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101.

**Table 48. Incidence of QT interval prolongation (patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101)**

| PT (MedDRA ver.20.1) | Number of subjects (%) | | | |
|---|---|---|---|---|
| | U201 n = 184 | | J101 n = 50 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| QT interval prolongation | 8 (4.3) | 1 (0.5) | 6 (12.0) | 1 (2.0) |
| Electrocardiogram QT prolonged | 8 (4.3) | 1 (0.5) | 5 (10.0) | 0 |
| Seizure | 0 | 0 | 1 (2.0) | 1 (2.0) |

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201, QT interval prolongation events led to dose interruption in 2 of 184 subjects (1.1%; electrocardiogram QT prolonged [2]). No QT interval prolongation events led to death, or serious QT interval prolongation were reported. No QT interval prolongation events led to treatment discontinuation or dose reduction.

In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study J101, a serious event of QT interval prolongation occurred in 1 of 50 subjects (2.0%; seizure), and a causal relationship to trastuzumab deruxtecan was denied. An event of QT interval prolongation led to dose interruption in 1 of 50 subjects (2.0%; seizure). No events of QT interval prolongation led to death, treatment discontinuation, or dose reduction.

Median time to first onset of QT interval prolongation events was 81.5 days (range, 21-350) in Study U201, and 35.0 days (range, 15-207) in Study J101.

Table 49 shows the change from baseline in QTcF associated with trastuzumab deruxtecan treatment in Studies U201 and J101. Of patients who showed change from baseline in QTcF, no serious QT interval prolongation-related symptoms were observed.

**Table 49. Change in QTcF associated with trastuzumab deruxtecan treatment (pooled data from Studies U201 and J101)**

| | Number of subjects (%) n = 234 |
|---|---|
| Maximum value | |
| >480 ms | 13 (5.6) |
| >500 ms | 2 (0.9) |
| >550 ms | 1 (0.4) |
| Increase in change from baseline (maximum value) | |
| >30 ms | 39 (16.7) |
| >60 ms | 8 (3.4) |
| >100 ms | 1 (0.4) |
| Mean increase in change from baseline (maximum value) [90% CI] | 16.4 ms [14.1, 18.6] |

(c) Tumour lysis syndrome

To evaluate tumour lysis syndrome, events classified as MedDRA PTs "tumour lysis syndrome," "tumor necrosis," and "haemorrhagic tumour necrosis" were captured.

No tumour lysis syndrome occurred in patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Study U201 or J101.

In all the ongoing and past clinical studies of trastuzumab deruxtecan, a serious event of tumour lysis syndrome associated with trastuzumab deruxtecan occurred in 1 patient with details shown in Table 50.

**Table 50. Details of the patient who developed a serious event of tumour lysis syndrome**

| Trastuzumab deruxtecan dose (mg/kg) | Study | Age | Sex | Primary disease | PT (MedDRA ver.20.1) | Grade | Onset (days) | Duration (days) | Trastuzumab deruxtecan treatment | Causal relation-ship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.4 | J101 | 58 | M | Colorectal cancer | Tumour lysis syndrome | 3 | 57 | 5 | Continued | Yes | Resolved |

PMDA's discussion:

As shown in subsections (a) through (c) above, a causal relationship to trastuzumab deruxtecan could not be ruled out for some events that occurred in the clinical studies. In light of the current situation where the number of serious adverse events is limited, no special cautionary advice will be necessary. However, taking into consideration that these have already been identified as risks for conventional HER2-targeted drugs, PMDA concluded that data should be gathered continuously in the post-marketing setting, and any new useful findings should be provided to healthcare professionals in an appropriate manner.

### 7.R.4 Clinical positioning and indication

The proposed indication of trastuzumab deruxtecan was specified as "unresectable or recurrent HER2-positive breast cancer previously treated with trastuzumab emtansine (genetical recombination)." The "Precautions Concerning Indication" section included a statement to the effect that the efficacy and safety of trastuzumab deruxtecan in a neoadjuvant or adjuvant chemotherapy have not been established.

However, after the application was filed, the applicant explained that the statements in the "Precautions Concerning Indication" section would be modified as shown below:

- The efficacy and safety of trastuzumab deruxtecan in patients previously treated with ≤1 regimen of HER2-targeted therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy have not been established.

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)," and at the same time, to include the following cautionary statements in the "Precautions Concerning Indication" section:

- The efficacy and safety of trastuzumab deruxtecan in patients who have not previously received trastuzumab (genetical recombination), taxane-based chemotherapy, and trastuzumab emtansine (genetical recombination) have not been established.
- The efficacy and safety of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

#### 7.R.4.1 Clinical positioning of trastuzumab deruxtecan and indication

In the latest clinical practice guidelines and representative textbooks of clinical oncology published in Japan and other countries, no descriptions of trastuzumab deruxtecan were found.

The applicant's explanation about clinical positioning and indication of trastuzumab deruxtecan:
The results of Studies U201 and J101 suggest that trastuzumab deruxtecan can be positioned as a treatment option for patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1. In light of the current situation where no clinical study data have been obtained regarding the efficacy and safety of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy, the use of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy is not recommended.

On the basis of the above, the proposed indication of trastuzumab deruxtecan was specified as "unresectable or recurrent HER2-positive breast cancer previously treated with trastuzumab emtansine (genetical recombination)" while giving precautionary statement in the "Precautions Concerning Indication" section to the effect that the efficacy and safety of trastuzumab deruxtecan [neo] adjuvant chemotherapy have not been established.

No data from clinical studies have been obtained to compare the efficacy and safety of trastuzumab deruxtecan with those of conventional therapies, i.e., lapatinib plus capecitabine or trastuzumab plus capecitabine in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1, and therefore the choice between trastuzumab deruxtecan and the conventional therapy is currently unclear. Ongoing clinical studies include a global phase III study (Study U301) shown below.

- An open-label, randomized study to compare the efficacy and safety of trastuzumab deruxtecan versus lapatinib plus capecitabine or trastuzumab plus capecitabine in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 (target sample size, 600 subjects).

All 253 patients enrolled in Study U201 were previously treated not only with T-DM1, but also with trastuzumab; therefore, PMDA asked the applicant to explain the clinical benefit of trastuzumab deruxtecan in patients who were previously treated with T-DM1 but not received other HER2-targeted therapies.

The applicant's response:

Taking into consideration that no criteria were specified in Study U201 with regard to prior treatment other than T-DM1, and that in clinical practice guidelines published in Japan and other countries, T-DM1 is also recommended as first line therapy[59)] for patients with unresectable or recurrent HER2-positive breast cancer, trastuzumab deruxtecan may offer a new treatment option for patients who have previously received T-DM1 but have not received other HER2-targeted therapies. However, of patients evaluated in Study U201 and Part 2a of Study J101, only 1 patient had not received prior HER2-targeted therapy other than T-DM1, and furthermore, the efficacy of trastuzumab deruxtecan in this particular patient has not been clarified. It is therefore considered appropriate to provide information on prior therapies of patients in Study U201 and Part 2a of Study J101 in the "Clinical Studies" section of the package insert, and include the cautionary statement shown below in the "Precautions Concerning Indication" section:

- The efficacy and safety of trastuzumab deruxtecan in patients previously treated with ≤1 regimen of anti-HER2 therapy have not been established.

PMDA's discussion:

PMDA largely accepted the applicant's explanation above. However, confirmatory study results of trastuzumab deruxtecan in patients with unresectable or recurrent HER2-positive breast cancer have not been obtained. Considering this and other factors, it is not recommended to give priority to trastuzumab deruxtecan over (i) trastuzumab and a taxane-based chemotherapy regimen, a standard first-line

59) In a foreign phase III study (MARIANNE study) conducted to evaluate the efficacy and safety of T-DM1 with or without pertuzumab versus trastuzumab plus taxane-based chemotherapy in patients with unresectable or recurrent HER2-positive breast cancer previously untreated with chemotherapy, compared with the control group, in terms of outcome, T-DM1 monotherapy did not have an effect on the survival of patients; however, the results on the incidence of Grade ≥3 adverse events and QOL were favorable (*J Clin Oncol.* 2017;35:141-8). On the basis of the findings, in the Clinical Practice Guidelines for Breast Cancer in Japan, a weak recommendation has been made for the T-DM1 monotherapy in the patient population of the study.

treatment regimen; and (ii) T-DM1, a standard second-line treatment regimen. Therefore, PMDA concluded that it is appropriate to state clearly in the "Indication" that trastuzumab deruxtecan is indicated for the treatment of patients ineligible for standard lines of treatment, and to provide caution in the "Precautions Concerning Indication" section to the effect that the efficacy and safety of trastuzumab deruxtecan in patients who have not received prior treatment with trastuzumab, taxane-based chemotherapy, and T-DM1 have not established.

In addition to the above, in the present application, the efficacy of trastuzumab deruxtecan was evaluated primarily based on the results of objective response rate, while information on the effects on patient survival has not been obtained. Because other treatment options should also be carefully considered, PMDA concluded that it is appropriate to provide caution in the "Precautions Concerning Indication" section to the effect that whether a patient is eligible for treatment with trastuzumab deruxtecan should be carefully determined only after a thorough consideration of other treatment options.

On the basis of the above, PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)," and include in the "Precautions Concerning Indication" section the cautionary statements shown below.

- The efficacy and safety of trastuzumab deruxtecan in patients who have not previously received trastuzumab (genetical recombination), taxane-based chemotherapy, and trastuzumab emtansine (genetical recombination) have not been established.
- The efficacy and safety of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

PMDA concluded that data should be continuously collected from studies including the ongoing Study U301 to gain useful information on the choice between trastuzumab deruxtecan and conventional therapies, e.g., lapatinib plus capecitabine or trastuzumab plus capecitabine, and when new information becomes available, it is necessary to take appropriate action including providing information to healthcare professionals.

### 7.R.5 Dosage and administration

The proposed dosage and administration of trastuzumab deruxtecan was "The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion every 3 weeks." In the "Precautions Concerning Dosage and Administration" section, the following statements were specified:

- The efficacy and safety of trastuzumab deruxtecan in combination with other antineoplastic agents have not been established.
- Administer the first dose as an intravenous infusion over 90 minutes. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.
- Dose interruption, reduction, or treatment discontinuation of trastuzumab deruxtecan for adverse reactions.

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the dosage and administration of trastuzumab deruxtecan as "The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes." and at the same time, to include the following cautionary statements in the "Precautions Concerning Dosage and Administration" section.

- The efficacy and safety of trastuzumab deruxtecan in combination with other antineoplastic agents have not been established.
- Dose interruption, reduction, or treatment discontinuation of trastuzumab deruxtecan for adverse reactions.

#### 7.R.5.1 Dosage regimen of trastuzumab deruxtecan

The applicant's explanation of the rationale for selecting the proposed dosage and administration of trastuzumab deruxtecan:

Study U201 was conducted with the dosage and administration specified based on the clinical study results shown below and other information. The results of Study U201 demonstrated the clinical benefits of trastuzumab deruxtecan in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1. Based on the results and other data, the dosage and administration of trastuzumab deruxtecan for this application was proposed referring to the specifications of Part 2 of Study U201.

- In Part 1 of Study J101, trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg was administered intravenously Q3W. While the MTD of trastuzumab deruxtecan was not determined, 5.4 and 6.4 mg/kg were selected as the dose levels for Part 2 of Study J101 taking the relationship between efficacy/safety and exposure into account.
- On the basis of the results of a comparison of the efficacy and safety in the 5.4 mg/kg group and in the 6.4 mg/kg group in Part 1 of Study U201, trastuzumab deruxtecan 5.4 mg/kg intravenously Q3W was specified as the recommended dose for Part 2 of Study U201.

PMDA's discussion:

PMDA largely accepted the applicant's explanation above. However, it is appropriate to clearly state the infusion time of trastuzumab deruxtecan used in Study U201 in the "Dosage and Administration"

section. It is therefore appropriate to specify the dosage and administration as “The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.”

### 7.R.5.2 Dose modification of trastuzumab deruxtecan

The applicant’s explanation of the dose modification of trastuzumab deruxtecan:

Specific criteria for dose interruption, reduction, and treatment discontinuation of trastuzumab deruxtecan, which were prepared by making the revisions shown below to the criteria for dose interruption, reduction, and treatment discontinuation specified for Study U201, as well as specific treatment for adverse reactions will be specified in the “Precautions Concerning Dosage and Administration” section.

- Dose modification criteria were specified in Study U201 for adverse events including IRR, white blood cell count decreased, lymphocyte count decreased, anaemia, platelet count decreased, QT interval prolongation, troponin T increased, eye disorders, renal dysfunction, hepatic dysfunction, gastrointestinal disorders, and laboratory abnormalities; however, these criteria will not be specified taking into account the incidence of serious adverse events, and adverse events leading to dose interruption that occurred in the clinical studies.
- According to the prespecified criteria on ILD in Studies U201 and J101, trastuzumab deruxtecan treatment was to be resumed after a Grade 1 ILD event had resolved. However, given that Grade 1 events of ILD occurred frequently in the clinical studies of trastuzumab deruxtecan; when Grade 1 events of ILD have occurred, as a general rule, trastuzumab deruxtecan treatment will be discontinued.
- In the clinical studies of trastuzumab deruxtecan, treatment of 3 subjects resumed after a Grade 1 ILD event had resolved, and no Grade ≥2 ILD events occurred. On the basis of such findings, trastuzumab deruxtecan treatment may be resumed only after carefully considering benefits and risks associated with trastuzumab deruxtecan treatment after the ILD events have resolved.
- In Studies U201 and J101, regarding the resumption of trastuzumab deruxtecan treatment after a Grade 1 ILD event has resolved, the criteria specified that treatment was to be resumed at the same dose level if recovery occurred within 28 days, and at 1 dose level lower if recovery occurred after >28 days. However, the necessity of dose reduction should be assessed independent of time to recovery; therefore, the specification will be revised to allow the physician to make decision based on the condition of the patient concerned.
- On the basis of the incidence of ILD in the clinical studies, death resulted from ILD, in which there was a prolonged period after the onset of ILD to the initiation of corticosteroid treatment, and other information, corticosteroid treatment should be considered for Grade 1 ILD events, and corticosteroid treatment should be initiated immediately after the onset of Grade ≥2 ILD.

PMDA's discussion:

PMDA largely accepted the applicant's explanation above. The ILD-related specific criteria for dose interruption, reduction, and treatment discontinuation of trastuzumab deruxtecan have been revised to more strict criteria compared to those specified for Studies U201 and J101 taking into consideration the incidence of ILD in the clinical studies of trastuzumab deruxtecan. However, given the findings shown below, it is not clear if it is appropriate to resume trastuzumab deruxtecan treatment after a Grade 1 ILD event has resolved. It was concluded that when ILD has occurred, it is appropriate to discontinue treatment regardless of the grade.

- Only 3 patients resumed treatment with trastuzumab deruxtecan after a Grade 1 ILD event had resolved.
- In patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies U201 and J101, ILD led to death in 4 of 184 subjects (2.2%) and serious ILD occurred in 4 of 184 (2.2%) in Study U201, while ILD led to death in 2 of 50 subjects (4.0%) and serious ILD occurred in 4 of 50 subjects (8.0%) in Study J101.
- In Japanese patients who received trastuzumab deruxtecan 5.4 mg/kg in the clinical studies of trastuzumab deruxtecan, no ILD events led to death. However, in Japanese patients who received trastuzumab deruxtecan 6.4 mg/kg, ILD events led to death in 3 subjects.
- Of Grade 1 and 2 ILD events reported in the clinical studies of trastuzumab deruxtecan, deaths occurred in patients who developed ILD events classified as the OP-like pattern, which accounted for 85.7%.

PMDA concluded that it is appropriate to specify the criteria shown below which were prepared based on the criteria for dose interruption, reduction, and treatment discontinuation specified for Study U201 in the "Precautions Concerning Dosage and Administration" section, and to provide information regarding specific treatments in the event of onset of ILD in the section other than the "Precautions Concerning Dosage and Administration" section of the package insert or other materials.

- If the patient develops an adverse reaction following administration of trastuzumab deruxtecan, the dose of trastuzumab deruxtecan must be interrupted, reduced, or treatment with trastuzumab deruxtecan must be discontinued based on the following criteria.

**Dose levels for reductions and treatment discontinuation**

| Dose reduction level | Dose |
|---|---|
| Usual dose | 5.4 mg/kg |
| First dose reduction | 4.4 mg/kg |
| Second dose reduction | 3.2 mg/kg |
| Treatment discontinuation | If 3.2 mg/kg is not tolerated, discontinue treatment |

**Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions**

| Adverse reaction | Severity[Note] | | Action |
|---|---|---|---|
| ILD | | | Discontinue treatment. |
| LVEF decreased | LVEF ≥40% and ≤45% | Absolute decrease from baseline is <10% | Consider dose interruption. Repeat LVEF assessment within 3 weeks. |
| | | Absolute decrease from baseline is ≥10% and ≤20% | Interrupt dose, and repeat LVEF assessment within 3 weeks. If the absolute decrease in LVEF from baseline has not recovered to <10%, discontinue treatment. |
| | LVEF < 40% or absolute decrease from baseline is >20% | | Interrupt dose, and repeat LVEF assessment within 3 weeks. If LVEF remains <40%, or absolute decrease from baseline is >20%, discontinue treatment. |
| Symptomatic congestive heart failure | | | Discontinue treatment. |
| QT interval prolongation | Grade 3 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| IRR | Grade 1 | | Reduce infusion rate by 50%.<br>If no other symptoms develop, administer at the original infusion rate in subsequent infusions. |
| | Grade 2 | | Temporarily stop treatment until resolved to Grade ≤1. If treatment is resumed, reduce infusion rate by 50%. Administer at the reduced infusion rate in subsequent infusions. |
| | Grade 3 or 4 | | Discontinue treatment. |
| Neutrophil count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. Or, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Febrile neutropenia | | | Interrupt dose until resolved. After resolved, reduce dose by 1 level, and resume treatment. |
| Anaemia | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Platelet count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level, and resume treatment. |
| Total bilirubin increased | Grade 2 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, reduce dose by 1 level, and resume treatment.<br>If resolved in >7 days, discontinue treatment. |
| | Grade 4 | | Discontinue treatment. |
| Diarrhoea or colitis | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤3 days, resume treatment at the same dose level.<br>If resolved in >3 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| Other adverse reactions | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |

Note, toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

### 7.R.6 Post-marketing investigations

The applicant's explanation on the post-marketing investigations:

Given the findings including the higher incidence of ILD in Japanese patients among patients with unresectable or recurrent HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies J101 and U201, the applicant has planned to conduct post-marketing surveillance to keep track of the occurrence of ILD in clinical practice, and investigate risk factors, while defining ILD as a safety specification. This planned surveillance will cover all patients who will be receiving trastuzumab deruxtecan.

A planned sample size of 1,500 has been specified so as to allow comparison of characteristics of patients who have developed ILD with those who have not, as well as investigation of risk factors, taking into account the incidence of ILD or other data for patients with HER2-positive breast cancer who received trastuzumab deruxtecan 5.4 mg/kg in Studies J101 and U201.

A follow-up period of 18 months was selected taking into account the time to onset of ILD being within 18 months of the start of trastuzumab deruxtecan treatment in patients with HER2-positive breast cancer who received trastuzumab deruxtecan in Studies J101 and U201.

PMDA's discussion:

Only limited safety data are available for trastuzumab deruxtecan treatment in Japanese patients. It was therefore concluded that post-marketing surveillance should be conducted, covering all patients who will be receiving trastuzumab deruxtecan for a specified period after the market launch, to gather safety data in an unbiased manner without delay, and the safety data so obtained should be provided promptly to healthcare professionals.

On the basis of the discussions in Section "7.R.3 Safety," the safety specification for the post-marketing surveillance should be as specified by the applicant because the investigation of risk factors for ILD is of primary importance.

## 7.2 Adverse events and other findings observed in clinical studies

The following sections discuss main adverse events from the results of clinical studies submitted for safety evaluation, except for those that resulted in death, which are discussed in Section "7.1 Evaluation data."

### 7.2.1 Japanese phase I study (Study J102)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥25% were nausea in 42 subjects (82.4%); neutrophil count decreased in 36 subjects (70.6%); white blood cell count decreased in 31 subjects (60.8%); anaemia in 30 subjects (58.8%); alopecia in 21 subjects (41.2%); vomiting and platelet count decreased in 20 subjects each (39.2%); decreased appetite,

constipation, and stomatitis in 16 subjects each (31.4%); diarrhoea in 14 subjects (27.5%); and lymphocyte count decreased in 13 subjects (25.5%).

Serious adverse events occurred in 2 of 51 subjects (3.9%). The reported serious adverse events were femur fracture and nausea in 1 subject each. A causal relationship to trastuzumab deruxtecan could not be ruled out for the event of nausea.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 2 of 51 subjects (3.9%). The reported adverse events leading to treatment discontinuation were pneumonitis and ejection fraction decreased in 1 subject each. A causal relationship to trastuzumab deruxtecan could not be ruled out for either of the events.

### 7.2.2 Global phase I study (Study J101)

#### 7.2.2.1 Part 1

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred in 3 of 3 subjects (100%) at 0.8 mg/kg; 2 of 3 subjects (66.7%) at 1.6 mg/kg; 2 of 3 subjects (66.7%) at 3.2 mg/kg; 6 of 6 subjects (100%) at 5.4 mg/kg; 6 of 6 subjects (100%) at 6.4 mg/kg; and 6 of 6 subjects (100%) at 8.0 mg/kg. Adverse events with an incidence of ≥50% in each dose group were as follows: at 0.8 mg/kg, nausea and fatigue in 3 subjects each (100%), decreased appetite, headache, and electrocardiogram QT prolonged in 2 subjects each (66.7%); at 3.2 mg/kg, nausea and vomiting in 2 subjects each (66.7%); at 5.4 mg/kg, nausea in 6 subjects (100%), decreased appetite, constipation, platelet count decreased, and neutrophil count decreased in 4 subjects each (66.7%), anaemia and white blood cell count decreased in 3 subjects each (50.0%); at 6.4 mg/kg, decreased appetite, nausea, and vomiting in 4 subjects each (66.7%), abdominal distension, alopecia, fatigue, and platelet count decreased in 3 subjects each (50.0%); at 8.0 mg/kg, nausea and fatigue in 4 subjects each (66.7%), diarrhoea, alopecia, and platelet count decreased in 3 subjects each (50.0%). At 1.6 mg/kg, no adverse events with an incidence of ≥50% occurred.

Serious adverse events occurred in 1 of 6 subjects (16.7%) at 5.4 mg/kg; 1 of 6 subjects (16.7%) at 6.4 mg/kg; and 1 of 6 subjects (16.7%) at 8.0 mg/kg. The reported serious adverse events by group were soft tissue infection and febrile neutropenia in 1 subject each (16.7%) at 5.4 mg/kg; cholangitis in 1 subject (16.7%) at 6.4 mg/kg; and intestinal perforation in 1 subject (16.7%) at 8.0 mg/kg. Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for febrile neutropenia in 1 subject at 5.4 mg/kg.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 1 of 6 subjects (16.7%) at 6.4 mg/kg and 3 of 6 subjects (50.0%) at 8.0 mg/kg. The reported adverse events leading to treatment discontinuation by group were platelet count decreased in 1 subject (16.7%) at 6.4 mg/kg; and pneumonia, pneumonitis, and platelet count decreased in 1 subject each (16.7%) at 8.0 mg/kg. Among

these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for platelet count decreased in 1 subject at 6.4 mg/kg and pneumonitis in 1 subject at 8.0 mg/kg.

#### 7.2.2.2 Part 2a

##### 7.2.2.2.1 5.4 kg/mg group

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Table 51 shows adverse events with an incidence of ≥20%.

**Table 51. Adverse events with an incidence of ≥20%**

| SOC<br>PT<br>(MedDRA ver.20.1) | Number of subjects (%)<br>n = 48 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 48 (100) | 21 (43.8) |
| Blood and lymphatic system disorders | | |
| Anaemia | 21 (43.8) | 4 (8.3) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 21 (43.8) | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 13 (27.1) | 0 |
| Gastrointestinal disorders | | |
| Nausea | 41 (85.4) | 2 (4.2) |
| Vomiting | 27 (56.3) | 2 (4.2) |
| Diarrhoea | 18 (37.5) | 1 (2.1) |
| Constipation | 18 (37.5) | 1 (2.1) |
| Skin and subcutaneous tissue disorders | | |
| Alopecia | 18 (37.5) | 0 |
| General disorders and administration site conditions | | |
| Fatigue | 24 (50.0) | 2 (4.2) |
| Oedema peripheral | 10 (20.8) | 0 |
| Investigations | | |
| Platelet count decreased | 13 (27.1) | 2 (4.2) |
| Neutrophil count decreased | 10 (20.8) | 4 (8.3) |

Serious adverse events occurred in 10 of 48 subjects (20.8%). Serious adverse events that occurred in ≥2 subjects were respiratory failure in 4 subjects (8.3%), pneumonitis in 3 subjects (6.3%), and pneumonia in 2 subjects (4.2%). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for pneumonitis in 3 subjects and respiratory failure in 1 subject.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 7 of 48 subjects (14.6%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 3 subjects (6.3%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for this event.

##### 7.2.2.2.2 6.4 kg/mg group

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥30% were nausea in 41 subjects (77.4%); decreased appetite in 40 subjects (75.5%); alopecia in 36

subjects (67.9%); vomiting in 29 subjects (54.7%); fatigue in 26 subjects (49.1%); diarrhoea in 25 subjects (47.2%); constipation in 23 subjects (43.4%); anaemia in 21 subjects (39.6%); neutrophil count decreased in 19 subjects (35.8%); malaise and AST increased in 17 subjects each (32.1%); and platelet count decreased and white blood cell count decreased in 16 subjects each (30.2%).

Serious adverse events occurred in 15 of 53 subjects (28.3%). Serious adverse events that occurred in ≥2 subjects were platelet count decreased in 3 subjects (5.7%) and pneumonitis in 2 subjects (3.8%). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for platelet count decreased and pneumonitis in 2 subjects each.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 19 of 53 subjects (35.8%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 7 subjects (13.2%), interstitial lung disease in 5 subjects (9.4%), and organising pneumonia in 2 subjects (3.8%). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for pneumonitis in 7 subjects, interstitial lung disease in 5 subjects, and organising pneumonia in 2 subjects.

#### 7.2.2.3 Part 2b

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred in 16 of 17 subjects (94.1%) at 5.4 mg/kg, and 24 of 24 subjects (100%) at 6.4 mg/kg. Adverse events with an incidence of ≥20% in each dose group were as follows: at 5.4 kg/mg, nausea in 10 subjects (58.8%); decreased appetite in 6 subjects (35.3%); platelet count decreased in 5 subjects (29.4%); anaemia, hypokalaemia, headache, and fatigue in 4 subjects each (23.5%); at 6.4 mg/kg, decreased appetite in 21 subjects (87.5%); nausea in 19 subjects (79.2%); anaemia in 13 subjects (54.2%); platelet count decreased and neutrophil count decreased in 11 subjects each (45.8%); white blood cell count decreased in 10 subjects (41.7%); pyrexia in 8 subjects (33.3%); vomiting and constipation in 7 subjects each (29.2%); dysgeusia and malaise in 5 subjects each (20.8%).

Serious adverse events occurred in 4 of 17 subjects (23.5%) at 5.4 mg/kg, and 6 of 24 subjects (25.0%) at 6.4 mg/kg. Serious adverse events that occurred in ≥2 subjects in each dose group were pneumonia in 2 subjects (11.8%) at 5.4 mg/kg, and decreased appetite in 3 subjects (12.5%) at 6.4 mg/kg. Of these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for pneumonia in 1 subject at 5.4 mg/kg and decreased appetite in 2 subjects at 6.4 mg/kg.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 3 of 24 subjects (12.5%) at 6.4 mg/kg. No adverse events leading to treatment discontinuation occurred in ≥2 subjects.

#### 7.2.2.4 Part 2c

##### 7.2.2.4.1 5.4 kg/mg group

Adverse events occurred in 19 of 20 subjects (95.0%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for events in 19 of 20 subjects (95.0%). Table 52 shows adverse events with an incidence of ≥20%.

**Table 52. Adverse events with an incidence of ≥20%**

| SOC<br>PT<br>(MedDRA ver.20.1) | Number of subjects (%)<br>n = 20 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 19 (95.0) | 10 (50.0) |
| Blood and lymphatic system disorders | | |
| Anaemia | 6 (30.0) | 2 (10.0) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 7 (35.0) | 0 |
| Gastrointestinal disorders | | |
| Nausea | 14 (70.0) | 0 |
| Vomiting | 10 (50.0) | 0 |
| Diarrhoea | 8 (40.0) | 0 |
| Constipation | 6 (30.0) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Alopecia | 6 (30.0) | 0 |
| General disorders and administration site conditions | | |
| Fatigue | 11 (55.0) | 1 (5.0) |
| Oedema peripheral | 4 (20.0) | 0 |
| Investigations | | |
| White blood cell count decreased | 4 (20.0) | 2 (10.0) |

Serious adverse events occurred in 3 of 20 subjects (15.0%). No serious adverse events occurred in ≥2 subjects.

No adverse events led to treatment discontinuation of trastuzumab deruxtecan.

##### 7.2.2.4.2 6.4 kg/mg group

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥30% were nausea in 18 subjects (90.0%); alopecia in 14 subjects (70.0%); diarrhoea in 12 subjects (60.0%); decreased appetite, vomiting, and constipation in 9 subjects each (45.0%); anaemia, neutrophil count decreased, and white blood cell count decreased in 7 subjects each (35.0%); and stomatitis, malaise, and pyrexia in 6 subjects each (30.0%).

Serious adverse events occurred in 5 of 20 subjects (25.0%). No serious adverse events occurred in ≥2 subjects.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 4 of 20 subjects (20.0%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 3

subjects (15.0%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for any of the events.

#### 7.2.2.5 Part 2d

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥30% were nausea in 44 subjects (74.6%); decreased appetite in 35 subjects (59.3%); vomiting in 31 subjects (52.5%); anaemia in 23 subjects (39.0%); platelet count decreased in 22 subjects (37.3%); fatigue and neutrophil count decreased in 21 subjects each (35.6%); alopecia in 20 subjects (33.9%); and diarrhoea in 19 subjects (32.2%).

Serious adverse events occurred in 18 of 59 subjects (30.5%). Serious adverse events that occurred in ≥2 subjects were anaemia and febrile neutropenia in 3 subjects each (5.1%); and sepsis, decreased appetite, and platelet count decreased in 2 subjects each (3.4%). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for febrile neutropenia in 3 subjects; platelet count decreased in 2 subjects; and sepsis, anaemia, and decreased appetite in 1 subject each.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 5 of 59 subjects (8.5%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 2 subjects (3.4%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for either of the events.

#### 7.2.2.6 Part 2e

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Table 53 shows adverse events with an incidence of ≥25%.

**Table 53. Adverse events with an incidence of ≥25%**

| SOC<br>PT<br>(MedDRA ver.20.1) | Number of subjects (%)<br>n = 21 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 21 (100) | 17 (81.0) |
| Blood and lymphatic system disorders | | |
| Anaemia | 15 (71.4) | 9 (42.9) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 15 (71.4) | 4 (19.0) |
| Hypoalbuminaemia | 8 (38.1) | 2 (9.5) |
| Gastrointestinal disorders | | |
| Nausea | 15 (71.4) | 2 (9.5) |
| Vomiting | 8 (38.1) | 0 |
| Diarrhoea | 7 (33.3) | 1 (4.8) |
| Constipation | 10 (47.6) | 0 |
| Stomatitis | 11 (52.4) | 1 (4.8) |
| Skin and subcutaneous tissue disorders | | |
| Alopecia | 10 (47.6) | 0 |
| General disorders and administration site conditions | | |
| Fatigue | 7 (33.3) | 2 (9.5) |
| Malaise | 9 (42.9) | 0 |
| Pyrexia | 6 (28.6) | 0 |
| Investigations | | |
| Platelet count decreased | 15 (71.4) | 6 (28.6) |
| Neutrophil count decreased | 11 (52.4) | 7 (33.3) |
| White blood cell count decreased | 11 (52.4) | 7 (33.3) |
| AST increased | 11 (52.4) | 2 (9.5) |
| ALT increased | 8 (38.1) | 1 (4.8) |

Serious adverse events occurred in 9 of 21 subjects (42.9%). Serious adverse events that occurred in ≥2 subjects were platelet count decreased in 3 subjects (14.3%); and decreased appetite and pneumonitis in 2 subjects each (9.5%). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for platelet count decreased in 3 subjects, pneumonitis in 2 subjects, and decreased appetite in 1 subject.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 10 of 21 subjects (47.6%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 5 subjects (23.8%) and interstitial lung disease in 3 subjects (14.3%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for pneumonitis in 5 subjects and interstitial lung disease in 3 subjects.

### 7.2.3 Global phase I study (Study A104)

Adverse events occurred in 17 of 17 subjects (100%) in Cohort 1, and 22 of 23 subjects (95.7%) in Cohort 2, and a causal relationship to the study drug could not be ruled out for events in 17 of 17 subjects (100%) in Cohort 1, and 21 of 23 subjects (91.3%) in Cohort 2. Adverse events with an incidence of ≥30% in each cohort were as follows: in Cohort 1, nausea in 17 subjects (100%); decreased appetite in 13 subjects (76.5%); platelet count decreased in 9 subjects (52.9%); constipation and diarrhoea in 8 subjects each (47.1%); white blood cell count decreased and ALT increased in 7 subjects each (41.2%);

anaemia, alopecia, neutrophil count decreased, and AST increased in 6 subjects each (35.3%); in Cohort 2, nausea in 15 subjects (65.2%); decreased appetite in 9 subjects (39.1%); vomiting and neutrophil count decreased in 8 subjects each (34.8%); constipation, alopecia, and white blood cell count decreased in 7 subjects each (30.4%).

Serious adverse events occurred in 2 of 17 subjects (11.8%) in Cohort 1, and 3 of 23 subjects (13.0%) in Cohort 2. The reported serious adverse events were disease progression and pneumonitis in 1 subject each (5.9%) in Cohort 1; and sepsis, diarrhoea, ileus, nausea, vomiting, and pyrexia in 1 subject each (4.3%) in Cohort 2. Among these events, a causal relationship to the study drug could not be ruled out for pneumonitis in 1 subject in Cohort 1; and diarrhoea, nausea, and vomiting in 1 subject each in Cohort 2.

Adverse events led to treatment discontinuation of the study drug in 3 of 17 subjects (17.6%) in Cohort 1. The reported adverse events leading to treatment discontinuation were osteomyelitis, organising pneumonia, and pneumonitis in 1 subject each (5.9%), and a causal relationship to the study drug could not be ruled out for the events of pneumonitis and organising pneumonia.

### 7.2.4 Global phase II study (Study U201)

#### 7.2.4.1 Part 1

##### 7.2.4.1.1 PK stage

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥25% in each dose group were as follows: at 5.4 mg/kg, nausea in 17 subjects (77.3%); alopecia in 12 subjects (54.5%); vomiting, fatigue, and neutrophil count decreased in 11 subjects each (50.0%); white blood cell count decreased in 9 subjects (40.9%); anaemia in 8 subjects (36.4%); decreased appetite in 7 subjects (31.8%); constipation and stomatitis in 6 subjects each (27.3%); at 6.4 mg/kg, nausea in 17 subjects (77.3%); anaemia in 14 subjects (63.6%); alopecia, white blood cell count decreased, and neutrophil count decreased in 12 subjects each (54.5%); decreased appetite and fatigue in 11 subjects each (50.0%); constipation, stomatitis, and platelet count decreased in 7 subjects each (31.8%); vomiting in 6 subjects (27.3%); at 7.4 mg/kg, nausea and white blood cell count decreased in 13 subjects each (61.9%); neutrophil count decreased in 12 subjects (57.1%); fatigue in 11 subjects (52.4%); anaemia and constipation in 10 subjects each (47.6%); alopecia in 8 subjects (38.1%); vomiting, platelet count decreased, ALT increased, and AST increased in 7 subjects each (33.3%); decreased appetite and blood alkaline phosphatase (ALP) increased in 6 subjects each (28.6%).

Serious adverse events occurred in 3 of 22 subjects (13.6%) at 5.4 mg/kg; 5 of 22 subjects (22.7%) at 6.4 mg/kg; and 8 of 21 subjects (38.1%) at 7.4 mg/kg. Serious adverse events that occurred in ≥2 subjects in each dose group were ALT increased and AST increased in 2 subjects each (9.5%) at 7.4 mg/kg. Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for ALT increased and AST increased in 1 subject each.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 2 of 22 subjects (9.1%) at 5.4 mg/kg; 5 of 22 subjects (22.7%) at 6.4 mg/kg; and 8 of 21 subjects (38.1%) at 7.4 mg/kg. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each dose group were pneumonitis in 2 subjects (9.1%) at 5.4 mg/kg; interstitial lung disease in 2 subjects (9.1%) at 6.4 mg/kg; and interstitial lung disease in 4 subjects (19.0%) and pneumonitis in 2 subjects (9.5%) at 7.4 mg/kg. A causal relationship to trastuzumab deruxtecan could not be ruled out for any of the events.

#### 7.2.4.1.1 Dose finding stage

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred in 28 of 28 subjects (100%) at 5.4 mg/kg, and 25 of 26 subjects (96.2%) at 6.4 mg/kg. Adverse events with an incidence of ≥25% were as follows: at 5.4 mg/kg, nausea in 21 subjects (75.0%); alopecia in 13 subjects (46.4%); vomiting in 12 subjects (42.9%); diarrhoea in 11 subjects (39.3%); constipation and fatigue in 10 subjects each (35.7%); anaemia and decreased appetite in 8 subjects each (28.6%); asthenia in 7 subjects (25.0%); at 6.4 mg/kg, nausea in 23 subjects (88.5%); alopecia in 16 subjects (61.5%); vomiting and fatigue in 13 subjects each (50.0%); decreased appetite and constipation in 10 subjects each (38.5%); diarrhoea in 8 subjects (30.8%); and asthenia in 7 subjects (26.9%).

Serious adverse events occurred in 8 of 28 subjects (28.6%) at 5.4 mg/kg, and 1 of 26 subjects (3.8%) at 6.4 mg/kg. Serious adverse events that occurred in ≥2 subjects in each dose group were cellulitis in 3 subjects (10.7%) and pleural effusion in 2 subjects (7.1%) at 5.4 mg/kg, and a causal relationship to trastuzumab deruxtecan could not be ruled out for cellulitis in 2 subjects.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 4 of 28 subjects (14.3%) at 5.4 mg/kg, and 1 of 26 subjects (3.8%) at 6.4 mg/kg. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each dose group were pneumonitis in 2 subjects (7.1%) at 5.4 mg/kg, and a causal relationship to trastuzumab deruxtecan could not be ruled out for either of the events.

### 7.2.4.2 Part 2a

Adverse events occurred in 129 of 130 subjects (99.2%). Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred in 128 of 130 subjects (98.5%). Table 54 shows adverse events with an incidence of ≥15%.

**Table 54. Adverse events with an incidence of ≥15%**

| SOC<br>PT<br>(MedDRA ver.20.1) | Number of subjects (%)<br>n = 130 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 129 (99.2) | 63 (48.5) |
| Nervous system disorders | | |
| Headache | 26 (20.0) | 0 |
| Blood and lymphatic system disorders | | |
| Anaemia | 31 (23.8) | 7 (5.4) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 37 (28.5) | 3 (2.3) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 23 (17.7) | 0 |
| Gastrointestinal disorders | | |
| Nausea | 101 (77.7) | 11 (8.5) |
| Vomiting | 58 (44.6) | 4 (3.1) |
| Constipation | 46 (35.4) | 1 (0.8) |
| Diarrhoea | 33 (25.4) | 1 (0.8) |
| Skin and subcutaneous tissue disorders | | |
| Alopecia | 61 (46.9) | 1 (0.8) |
| General disorders and administration site conditions | | |
| Fatigue | 65 (50.0) | 9 (6.9) |
| Investigations | | |
| Neutrophil count decreased | 21 (16.2) | 10 (7.7) |
| White blood cell count decreased | 20 (15.4) | 4 (3.1) |

Serious adverse events occurred in 25 of 130 subjects (19.2%). Serious adverse events that occurred in ≥2 subjects were intestinal obstruction, nausea, and pneumonia in 3 subjects each (2.3%); and vomiting, abdominal pain, hypokalaemia, and urinary tract infection in 2 subjects each. Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for nausea in 3 subjects; vomiting in 2 subjects; and pneumonia and hypokalaemia in 1 subject each.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 8 of 130 subjects (6.2%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were pneumonitis in 3 subjects (2.3%), and a causal relationship to trastuzumab deruxtecan could not be ruled out for either of the events.

#### 7.2.4.3 Part 2b

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Table 55 shows adverse events with an incidence of ≥50%.

**Table 55. Adverse events with an incidence of ≥50%**

| SOC<br>PT<br>(MedDRA ver.20.1) | Number of subjects (%)<br>n = 4 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 4 (100) | 1 (25.0) |
| Gastrointestinal disorders | | |
| Nausea | 3 (75.0) | 1 (25.0) |
| Vomiting | 2 (50.0) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Alopecia | 2 (50.0) | 0 |
| General disorders and administration site conditions | | |
| Fatigue | 2 (50.0) | 0 |

No serious adverse events occurred.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 1 of 4 subjects (25.0%), and the reported adverse event leading to treatment discontinuation was neuropathy peripheral in 1 subject (25.0%). A causal relationship to trastuzumab deruxtecan could not be ruled out.

### 7.2.5 Foreign phase I study (Study A103)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to trastuzumab deruxtecan could not be ruled out also occurred in all subjects. Adverse events with an incidence of ≥25% were platelet count decreased and nausea in 7 subjects each (58.3%); AST increased in 6 subjects (50.0%); white blood cell count decreased in 5 subjects (41.7%); anaemia, ALT increased, and decreased appetite in 4 subjects each (33.3%); and stomatitis, fatigue, blood bilirubin increased, and body weight decreased in 3 subjects each (25.0%).

Serious adverse events occurred in 2 of 12 subjects (16.7%), and the reported serious adverse events were febrile neutropenia and urinary tract infection in 1 subject each (8.3%). A causal relationship to trastuzumab deruxtecan could not be ruled out for febrile neutropenia in 1 subject.

No adverse events led to treatment discontinuation of trastuzumab deruxtecan.

## 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 investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that trastuzumab deruxtecan has a certain level of efficacy in the treatment of unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy where no other standard of care treatment option is available, and that trastuzumab deruxtecan has acceptable safety in view of its benefits. Trastuzumab deruxtecan is a drug with a new active ingredient, which binds to HER2, and its linker, upon internalization into the cell, undergoes hydrolysis, releasing MAAA-1181a. The released MAAA-1181a is thought to induce DNA damage, apoptosis, and other effects, leading to inhibition of tumor growth. Trastuzumab deruxtecan is clinically meaningful because it offers a new treatment option for patients with unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy where no other standard of care treatment option is available. PMDA considers that several issues including the indication and dosage and administration require further discussion.

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

**Review Report (2)**

February 14, 2020

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Enhertu for Intravenous Drip Infusion 100 mg |
| **Non-proprietary Name** | Trastuzumab Deruxtecan (Genetical Recombination) |
| **Applicant** | Daiichi Sankyo Company, Limited |
| **Date of Application** | September 9, 2019 |

**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. 8/20 dated December 25, 2008).

### 1.1 Efficacy

In a global phase II study (Study U201) in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1, the objective response rate (%) [95% CI] by ICR according to RECIST ver1.1, the primary endpoint of the study, was 60.6% [53.0, 67.8] (109 of 180 subjects) in the Enrolled Analysis Set, and 64.1% [56.3, 71.3] (107 of 167 subjects) in the Response Evaluable Set.

In view of the discussions in Section "7.R.2 Efficacy" in Review Report (1), the results, including the above objective response rate achieved following administration of trastuzumab deruxtecan, which is characterized by a high DAR, demonstrate that trastuzumab deruxtecan has a certain level of efficacy in the treatment of patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1.

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

### 1.2 Safety

In view of the discussions in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that adverse events that require particular attention when trastuzumab deruxtecan is used in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 are ILD, myelosuppression, IRR, hepatic dysfunction, and cardiac disorder.

Although the use of trastuzumab deruxtecan requires particular caution for the adverse events mentioned above, PMDA concluded that patients should be able to tolerate trastuzumab deruxtecan provided that appropriate steps including monitoring and control of adverse events and dose modification are taken by a physician with sufficient knowledge and experience in cancer chemotherapy, and that safety management measures can be ensured by utmost attention and control measures for serious adverse events including ILD.

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" of Review Report (1), PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)," and at the same time, to include the following cautionary statements in the "Precautions Concerning Indication" section:

**Precautions Concerning Indication**

- The efficacy and safety of trastuzumab deruxtecan in patients who have not previously received trastuzumab (genetical recombination), taxane-based chemotherapy, and trastuzumab emtansine (genetical recombination) have not been established.
- The efficacy and safety of trastuzumab deruxtecan as a neoadjuvant or adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

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

- Information on the clinical positioning of trastuzumab deruxtecan should be presented in a clear and easily understandable manner using suitable materials, taking into consideration the standard lines of treatment for unresectable or recurrent HER2-positive breast cancer so that patients eligible for trastuzumab deruxtecan treatment can be appropriately identified.

PMDA's discussion:

On the basis of the comment from the expert advisor, PMDA concluded that it is necessary to present the following information in a clear and easily understandable manner using suitable materials: information concerning standard lines of treatment for unresectable or recurrent HER2-positive breast

cancer; clinical positioning of trastuzumab deruxtecan; and other treatment options that are thought to have similar clinical positioning in the current treatment practice.

In conclusion, PMDA instructed the applicant to specify the "Indication" and the "Precautions Concerning Indication" sections as shown above and present information necessary to identify patients eligible for trastuzumab deruxtecan treatment in a clear and easily understandable manner. The applicant agreed with the instruction.

### 1.4 Dosage and administration

In view of the discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration of trastuzumab deruxtecan should be specified as "The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes." and at the same time, to include the following cautionary statements in the "Precautions Concerning Dosage and Administration" section.

**Precautions Concerning Dosage and Administration**

- The efficacy and safety of trastuzumab deruxtecan in combination with other antineoplastic agents have not been established.
- If the patient develops an adverse reaction following administration of trastuzumab deruxtecan, the dose of trastuzumab deruxtecan must be interrupted, reduced, or treatment with trastuzumab deruxtecan must be discontinued based on the following criteria.

**Dose levels for reductions and treatment discontinuation**

| Dose reduction level | Dose |
|---|---|
| Usual dose | 5.4 mg/kg |
| First dose reduction | 4.4 mg/kg |
| Second dose reduction | 3.2 mg/kg |
| Treatment discontinuation | If 3.2 mg/kg is not tolerated, discontinue treatment |

**Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions**

| Adverse reaction | Severity[Note] | | Action |
|---|---|---|---|
| ILD | | | Discontinue treatment. |
| LVEF decreased | LVEF ≥40% and ≤45% | Absolute decrease from baseline is <10% | Consider dose interruption. Repeat LVEF assessment within 3 weeks. |
| | | Absolute decrease from baseline is ≥10% and ≤20% | Interrupt dose, and repeat LVEF assessment within 3 weeks. If the absolute decrease in LVEF from baseline has not recovered to <10%, discontinue treatment. |
| | LVEF < 40% or absolute decrease from baseline is >20% | | Interrupt dose, and repeat LVEF assessment within 3 weeks. If LVEF remains <40%, or absolute decrease from baseline is >20%, discontinue treatment. |
| Symptomatic congestive heart failure | | | Discontinue treatment. |
| QT interval prolongation | Grade 3 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| IRR | Grade 1 | | Reduce infusion rate by 50%.<br>If no other symptoms develop, administer at the original infusion rate in subsequent infusions. |
| | Grade 2 | | Temporarily stop treatment until resolved to Grade ≤1. If treatment is resumed, reduce infusion rate by 50%. Administer at the reduced infusion rate in subsequent infusions. |
| | Grade 3 or 4 | | Discontinue treatment |
| Neutrophil count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. Or, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Febrile neutropenia | | | Interrupt dose until resolved. After resolved, reduce dose by 1 level, and resume treatment. |
| Anaemia | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Platelet count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level, and resume treatment. |
| Total bilirubin increased | Grade 2 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, reduce dose by 1 level, and resume treatment.<br>If resolved in >7 days, discontinue treatment. |
| | Grade 4 | | Discontinue treatment. |
| Diarrhoea or colitis | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤3 days, resume treatment at the same dose level.<br>If resolved in >3 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| Other adverse reactions | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |

Note, toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

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

- In light of the current situation of clinical practice, it is difficult to conduct chest CT scans frequently for the purpose of early detection of ILD associated with trastuzumab deruxtecan; therefore, regular chest X-rays are also recommended when trastuzumab deruxtecan is used.

On the basis of the above, PMDA instructed the applicant to specify the "Dosage and Administration" and the "Precaution Concerning Dosage and Administration" sections as shown above, and provide caution to the effect that when trastuzumab deruxtecan is used, regular chest X-rays need to be performed. The applicant agreed with the instruction.

### 1.5 Risk management plan (draft)

The applicant has planned to conduct post-marketing surveillance covering all patients who will be receiving trastuzumab deruxtecan with a planned sample size of 1,500 patients and a follow-up period of 18 months to keep track of the occurrence of ILD in clinical practice, and to investigate risk factors.

In view of the discussions in Section "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that a survey should be conducted, covering all patients who will be receiving trastuzumab deruxtecan for a specified period after the market launch, to gather safety data in an unbiased manner without delay, and the safety data so obtained should be provided promptly to healthcare professionals. PMDA also determined that the safety specification, planned sample size, and follow-up period for the post-marketing surveillance proposed by the applicant are acceptable.

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

On the basis of the above discussions, PMDA concluded that the current risk management plan (draft) for trastuzumab deruxtecan should include the safety specification presented in Table 56, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 57 and 58.

**Table 56. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • ILD<br>• Myelosuppression<br>• IRR | • Cardiac dysfunction (cardiac failure, LVEF decreased)<br>• Hepatic dysfunction<br>• Embryo-fetal toxicities | None |
| Efficacy specification | | |
| None | | |

**Table 57. Summary of additional pharmacovigilance activities, surveillance/studies on efficacy, and additional risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Surveillance/studies on efficacy | Additional risk minimization activities |
|---|---|---|
| • Early post-marketing phase vigilance<br>• Specified drug use-results survey (all-case surveillance)<br>• Post-marketing clinical study in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 (extension study of U201 Part 2a) | None | • Disseminate data gathered during early post-marketing phase vigilance<br>• Disseminate information promptly regarding the latest status of ILD occurrence<br>• Organize and disseminate information materials for healthcare professionals<br>• Organize and disseminate information materials for patients |

**Table 58. Outline of post-marketing surveillance plan (draft)**

| | |
|---|---|
| Objective | To keep track of the occurrence of ILD in clinical practice, and investigate risk factors |
| Survey method | All case surveillance |
| Population | All patients who have received trastuzumab deruxtecan |
| Follow-up period | 18 months |
| Planned sample size | 1,500 patients |
| Main survey items | Safety specification: ILD<br>Other main survey items: patient characteristics (e.g., sex, age, current/past smoking status, prior treatment for primary disease, medical history, complications), status of treatment with trastuzumab deruxtecan |

## 1.6 Other

### 1.6.1 Specification of the shelf life for the formulation

Additional data from the long-term study as of Month [redacted] have been submitted by the applicant. These are the testing results of 1 batch of the formulation manufactured by Process 3, and the long-term study results of this batch up to [redacted] months had been obtained earlier.

Although the proposed manufacturing process is the same as the manufacturing method for Process 3, the batch analysis indicated that the water content of the formulation manufactured by the proposed manufacturing process tended to be higher than that of the formulation manufactured by Process 3. PMDA asked the applicant to explain whether it is appropriate to specify the shelf life of the formulation manufactured by the proposed manufacturing process to be 24 months based on the testing results of the formulation manufactured by Process 3.

The applicant's response:

Taking into consideration factors including the following, water content has only a limited effect on the stability of the formulation, and therefore, the shelf life of the formulation manufactured by the proposed manufacturing process can be determined to be 24 months based on the testing results of the formulation manufactured by Process 3.

- Formulations with a target water content of [redacted]% and [redacted]% were subjected to accelerated testing conditions (25°C/60%RH), and changes in the quality of the formulations were compared. Both formulations remained similarly stable up to [redacted] months for the parameters studied.
- In the long-term stability testing up to [redacted] months, no differences have been noted in the trends of change between the 2 batches of the formulation manufactured by the proposed manufacturing

process (water content, [redacted]% and [redacted]%) and the 3 batches of the formulation manufactured by Process 3 (water content, [redacted]%, [redacted]%, and [redacted]%).

PMDA's discussion:
PMDA concluded that it is acceptable to specify the shelf life of the formulation manufactured by the proposed manufacturing process to be 24 months.

However, on the basis of several factors including the following, the decision as to whether the shelf life of the formulation manufactured by the proposed manufacturing process can be extended needs to be made based on the stability study data for the formulation. Therefore, PMDA concluded that the extension of shelf life based on the presented stability study data is not agreeable.

- Although it is within the range of specification, the [redacted] tended to decrease in 1 batch of the formulation manufactured by Process 3 as of Month 24.
- In the accelerated testing (25°C/60%RH) conducted using the formulations with a target water content of [redacted]% and [redacted]%, only the effects of different water content on physicochemical properties such as purity were investigated, but effects on biological activities have not been evaluated.

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

### 2.1 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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, it was confirmed that the study was generally conducted in compliance with GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issues at some trial sites. Although the issues had no significant impact on the overall assessment of the studies, the heads of the relevant medical institutions were notified of these issues as the findings requiring improvement:
Finding requiring corrective action
<u>Study sites</u>

- Protocol deviations (non-compliance with specifications on the dosage and administration of the study drug)

## 3. 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 shown below, with the conditions for approval shown below, provided that precautionary statement is included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and that trastuzumab deruxtecan is properly used only under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of providing adequate emergency medical care. Since trastuzumab deruxtecan is a drug with a new active ingredient, the re-examination period is 8 years, and is classified as a biological product. The drug substance and drug product are both classified as powerful drugs.

**Indication**

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

**Dosage and Administration**

The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to provide data on the efficacy and safety of the product from the ongoing phase III study in patients with unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy to healthcare professionals in an appropriate manner.
3. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been collected. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.

**Warnings**

1. The product should be administered only to patients who are considered eligible for its use under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of providing adequate emergency medical care. Prior to the start of therapy, the benefits and risks associated with the product (in particular, initial symptoms of interstitial lung disease, precautions during treatment, and information including reported fatal

cases) should be thoroughly explained to the patient or his/her family members and consent must be obtained.

2. The product should be used in cooperation with physicians with sufficient expertise in respiratory diseases because there have been reports of patients who died after experiencing interstitial lung disease associated with the product. During treatment, patients should be closely monitored for initial symptoms (e.g., dyspnea, cough, and pyrexia), and examined by regular $SpO_2$ level, chest X-ray, chest CT, and other tests. In the event of an abnormality being found, administration of the product should be discontinued and appropriate actions such as introduction of corticosteroid therapy should be taken.
3. Prior to the start of treatment with the product, the patient's eligibility for the treatment should be carefully determined after performing chest CT as well as patient interview, and confirming that the patient has no current or history of interstitial lung disease.

**Contraindication**

Patients with medical history of hypersensitivity to any of the excipients of the product

**Precautions Concerning Indication**

1. The efficacy and safety of the product in patients who have not previously received trastuzumab (genetical recombination), taxane-based chemotherapy, and trastuzumab emtansine (genetical recombination) have not been established.
2. The efficacy and safety of the product as a neoadjuvant or adjuvant therapy have not been established.
3. Whether a patient is eligible for treatment with the product should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of the product, while carefully examining other treatment options for the patient.

**Precautions Concerning Dosage and Administration**

1. The efficacy and safety of the product in combination with other antineoplastic agents have not been established.
2. If the patient develops an adverse reaction following administration of the product, the dose of the product must be interrupted, reduced, or treatment with the product must be discontinued based on the following criteria.

**Dose levels for reductions and treatment discontinuation**

| Dose reduction level | Dose |
|---|---|
| Usual dose | 5.4 mg/kg |
| First dose reduction | 4.4 mg/kg |
| Second dose reduction | 3.2 mg/kg |
| Treatment discontinuation | If 3.2 mg/kg is not tolerated, discontinue treatment. |

**Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions**

| Adverse reaction | Severity[Note)] | | Action |
|---|---|---|---|
| Interstitial lung disease | | | Discontinue treatment. |
| Left ventricular ejection fraction (LVEF) decreased | LVEF ≥40% and ≤45% | Absolute decrease from baseline is <10% | Consider dose interruption. Repeat LVEF assessment within 3 weeks. |
| | | Absolute decrease from baseline is ≥10% and ≤20% | Interrupt dose, and repeat LVEF assessment within 3 weeks. If the absolute decrease in LVEF from baseline has not recovered to <10%, discontinue treatment. |
| | LVEF < 40% or absolute decrease from baseline is >20% | | Interrupt dose, and repeat LVEF assessment within 3 weeks. If LVEF remains <40%, or absolute decrease from baseline is >20%, discontinue treatment. |
| Symptomatic congestive heart failure | | | Discontinue treatment. |
| QT interval prolongation | Grade 3 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| Infusion reaction | Grade 1 | | Reduce infusion rate by 50%.<br>If no other symptoms develop, administer at the original infusion rate in subsequent infusions. |
| | Grade 2 | | Temporarily stop treatment until resolved to Grade ≤1. If treatment is resumed, reduce infusion rate by 50%. Administer at the reduced infusion rate in subsequent infusions. |
| | Grade 3 or 4 | | Discontinue treatment. |
| Neutrophil count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. Or, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Febrile neutropenia | | | Interrupt dose until resolved. After resolved, reduce dose by 1 level, and resume treatment. |
| Anaemia | Grade 3 | | Interrupt dose until resolved to Grade ≤2. After resolved, resume treatment at the same dose level. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. |
| Platelet count decreased | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level, and resume treatment. |
| Total bilirubin increased | Grade 2 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, reduce dose by 1 level, and resume treatment.<br>If resolved in >7 days, discontinue treatment. |
| | Grade 4 | | Discontinue treatment. |
| Diarrhoea or colitis | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤3 days, resume treatment at the same dose level.<br>If resolved in >3 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |
| Other adverse reactions | Grade 3 | | Interrupt dose until resolved to Grade ≤1.<br>If resolved in ≤7 days, resume treatment at the same dose level.<br>If resolved in >7 days, reduce dose by 1 level, and resume treatment. |
| | Grade 4 | | Discontinue treatment. |

Note), toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ADC | antibody-drug conjugate |
| ADCC | antibody dependent cellular cytotoxicity |
| AKT | protein kinase B |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| application | application for marketing approval |
| AST | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| BCRP | breast cancer resistance protein |
| BID | bis in die |
| BSA | bovine serum albumin |
| BSEP | bile salt export pump |
| CAL | cells at the limit of *in vitro* cell age |
| [redacted] | [redacted] |
| [redacted]HPLC | [redacted]high-pressure liquid chromatography |
| CHK | cell cycle checkpoint kinase |
| CHO cell line | Chinese hamster ovary cell line |
| CI | confidence interval |
| CK | creatine phosphokinase |
| CLcr | creatinine clearance |
| $CL_{drug}$ | elimination clearance of released drug (MAAA-1181a) |
| Clinical Practice Guidelines for Breast Cancer in Japan | The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer 2018 |
| $CL_{intact}$ | elimination clearance of intact DS-8201a |
| CPP | critical process parameter |
| CQA | critical quality attribute |
| CR | complete response |
| CYP | cytochrome P450 |
| [redacted] | [redacted] |
| DAR | drug-to-antibody ratio |
| DLT | dose-limiting toxicity |
| [redacted] | [redacted] |
| DNA | deoxyribonucleic acid |
| ECL | electro-chemiluminescence |
| EDTA | ethylenediaminetetraacetic acid |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| FcRn | neonatal Fc receptor |
| FcγR | Fc gamma receptor |
| formulation manufactured by Process 3 | formulation manufactured by Process 3 |
| formulation manufactured by the proposed manufacturing process | formulation manufactured by the proposed manufacturing process |
| GC | gas chromatography |
| HCP | host cell protein |

| | |
|---|---|
| HER | human epidermal growth factor receptor |
| hERG | human *ether-a-go-go*-related gene |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICH Q1E Guidelines | "Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 3, 2003) |
| 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 Q5D Guidelines | Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873, dated July 14, 2000) |
| ICR | independent central review |
| Ig | immunoglobulin |
| IHC | immunohistochemistry |
| ILD | interstitial lung disease |
| IR | infrared absorption spectrum |
| IRR | infusion related reaction |
| ISH | *in situ* hybridization |
| $K_d$ | dissociation constant |
| $K_{rel}$ | release rate constant |
| lapatinib | lapatinib tosilate hydrate |
| lapatinib plus capecitabine | lapatinib in combination with capecitabine |
| LC | liquid chromatography |
| LC-MS/MS | liquid chromatography/tandem mass spectrometry |
| LDH | lactate dehydrogenase |
| LVEF | left ventricular ejection fraction |
| MATE | multidrug and toxin extrusion |
| MCB | master cell bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRNA | messenger ribonucleic acid |
| MRP | multidrug resistance associated protein |
| MTD | maximum tolerated dose |
| NADPH | nicotinamide adenine dinucleotide phosphate hydrogen |
| NCI-ODWG | National Cancer Institute Organ Dysfunction Working Group |
| NE | not evaluable |
| NGS | next generation sequencing |
| NHS | *N*-hydroxysuccinimide |
| NMR | nuclear magnetic resonance spectrum |
| [redacted] | [redacted] |
| OAT | organic anion transporter |
| OATP | organic anion transporting polypeptide |
| OCT | organic cation transporter |

| | |
|---|---|
| OS | overall survival |
| $P_{app\ A \rightarrow B}$ | apparent permeability coefficient value in apical to basolateral direction |
| $P_{app\ B \rightarrow A}$ | apparent permeability coefficient value in basolateral to apical direction |
| PARP | poly (ADP-ribose) polymerase |
| PBMC | peripheral blood mononuclear cell |
| PD | progressive disease |
| pertuzumab | pertuzumab (genetical recombination) |
| PFS | progression free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PPK | population pharmacokinetics |
| PPK/PD | population pharmacokinetics/pharmacodynamics |
| PR | partial response |
| PSL | photo-stimulated luminescence |
| PT | preferred term |
| QbD | quality by design |
| QD | quaque die |
| $Q_{intact}$ | intact DS-8201a inter-compartmental clearance |
| QOL | quality of life |
| QTcF | QT interval corrected with Fridericia's formula |
| Q3W | quaque 3 weeks |
| ΔQTcF | change from baseline in QT interval corrected with Fridericia's formula |
| [redacted] | [redacted] |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP-HPLC | reverse phase-high pressure liquid chromatography |
| SD | stable disease |
| SE-HPLC | size exclusion-high-pressure liquid chromatography |
| SMQ | standardised MedDRA queries |
| SOC | system organ class |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| Study A103 | Study DS8201-A-A103 |
| Study A104 | Study DS8201-A-A104 |
| Study J101 | Study DS8201-A-J101 |
| Study J102 | Study DS8201-A-J102 |
| Study U201 | Study DS8201-A-U201 |
| Study U301 | Study DS8201-A-U301 |
| T-DM1 | trastuzumab emtansine (genetical recombination) |
| total MAAL-9001 | sum of trastuzumab conjugated and unconjugated with MAAA-1181a |
| trastuzumab | trastuzumab (genetical recombination) |
| trastuzumab deruxtecan | trastuzumab deruxtecan (genetical recombination) |
| trastuzumab plus capecitabine | trastuzumab in combination with capecitabine |
| trastuzumab plus taxane-based chemotherapy | trastuzumab in combination with taxane-based chemotherapy |

| | |
|---|---|
| unconjugated MAAA-1181a | MAAA-1181a that is not linked to the antibody portion (MAAL-9001) |
| $V_{drug}$ | released drug (MAAA-1181a) volume of distribution |
| $V_{ss}$ | volume of distribution at steady state |
| $V_1$ | central volume of distribution |
| $V_2$ | peripheral volume of distribution |
| WCB | working cell bank |