Review Report

February 17, 2025
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	Rybrevant Intravenous Infusion 350 mg
Non-proprietary Name	Amivantamab (Genetical Recombination) (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 2024[1)]
Dosage Form/Strength	Injection: Each vial contains 350 mg of amivantamab (genetical recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product in combination with lazertinib mesilate hydrate is expected to have efficacy in the treatment of *EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer, and that the product in combination with lazertinib mesilate hydrate 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 indications and dosage and administration shown below, with the following condition.

Indications

EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer
<u>*EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer</u>

(Underline denotes additions.)

[1)] As of April 8, 2024, a marketing application for amivantamab as a drug with a new active ingredient was submitted for the indication of "*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer." Since amivantamab was approved for the indication of "*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer" as of September 24, 2024, a partial change application for a new indication and a new dosage was submitted.

Dosage and Administration

[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

The usual adult dosage of amivantamab (genetical recombination) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15	1,400 mg
	Cycle 2	Day 1	1,400 mg
	Cycle 3 onwards	Day 1	1,750 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,400 mg
		Day 8, Day 15	1,750 mg
	Cycle 2	Day 1	1,750 mg
	Cycle 3 onwards	Day 1	2,100 mg

[*EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

The usual adult dosage of amivantamab (genetical recombination) in combination with lazertinib mesilate is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	700 mg
		Day 8, Day 15, Day 22	1,050 mg
	Cycle 2 onwards	Day 1, Day 15	1,050 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15, Day 22	1,400 mg
	Cycle 2 onwards	Day 1, Day 15	1,400 mg

(Underline denotes additions.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

January 9, 2025

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).

Products Submitted for Approval

(1)

Brand Name Rybrevant Intravenous Infusion 350 mg

Non-proprietary Name Amivantamab (Genetical Recombination)

Applicant Janssen Pharmaceutical K.K.

Date of Application December 6, 2024[2)]

Dosage Form/Strength Injection: Each vial contains 350 mg of amivantamab (genetical recombination).

Proposed Indications

EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer

EGFR mutation-positive unresectable advanced or recurrent non-small cell lung cancer

(Underline denotes additions.)

Proposed Dosage and Administration

1. Patients with *EGFR* exon 20 insertion mutation-positive disease

The usual adult dosage of amivantamab (genetical recombination) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15	1,400 mg
	Cycle 2	Day 1	1,400 mg
	Cycle 3 onwards	Day 1	1,750 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,400 mg
		Day 8, Day 15	1,750 mg
	Cycle 2	Day 1	1,750 mg
	Cycle 3 onwards	Day 1	2,100 mg

2) As of April 8, 2024, a marketing application for amivantamab as a drug with a new active ingredient was submitted for the indication of "*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer." Since amivantamab was approved for the indication of "*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer" as of September 24, 2024, a partial change application for a new indication and a new dosage was submitted.

2. Patients with *EGFR* mutation-positive disease

The usual adult dosage of amivantamab (genetical recombination) in combination with lazertinib is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	700 mg
		Day 8, Day 15, Day 22	1,050 mg
	Cycle 2 onwards	Day 1, Day 15	1,050 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15, Day 22	1,400 mg
	Cycle 2 onwards	Day 1, Day 15	1,400 mg

(Underline denotes additions.)

(2)

Brand Name Lazcluze Tablets 80 mg, Lazcluze Tablets 240 mg

Non-proprietary Name Lazertinib Mesilate Hydrate

Applicant Janssen Pharmaceutical K.K.

Date of Application April 8, 2024

Dosage Form/Strength Tablets: Each tablet contains 96.48 mg or 289.44 mg lazertinib mesilate hydrate (equivalent to 80 mg or 240 mg, respectively, of lazertinib).

Proposed Indication

EGFR mutation-positive inoperable or recurrent non-small cell lung cancer

Proposed Dosage and Administration

The usual adult dosage is 240 mg of lazertinib orally once daily administered in combination with amivantamab (genetical recombination). The dosage should be reduced, as appropriate, according to the patient's condition.

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed products

Amivantamab (genetical recombination) (hereinafter referred to as Ami) is a recombinant protein (a bispecific antibody) with antigen-binding fragments targeting human epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition factor (MET), discovered by Genmab (Denmark) and Janssen Research & Development, LLC (the US). It binds to EGFR and MET and inhibits EGFR- and MET-mediated signaling. In addition, it induces antibody-dependent cellular cytotoxicity (ADCC) activity, etc. Ami is considered to inhibit tumor growth through these mechanisms.

Lazertinib mesilate hydrate (hereinafter referred to as Laz) is a small molecule inhibitor of EGFR, discovered by Genosco (the US) and Oscotec (Korea). It is considered to inhibit tumor growth by binding to EGFR and inhibiting EGFR phosphorylation and downstream signaling pathways.

In Japan, Ami was approved for the indication of "*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer (NSCLC)" in September 2024.

1.2 Development history, etc.

In the clinical development of Ami in combination with Laz (Ami/Laz) for the treatment of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, the applicant initiated the Ami/Laz cohort of a foreign phase I study in patients with unresectable advanced or recurrent NSCLC (Study EDI1001) in April 2019. Then the applicant initiated a global phase III study in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC (MARIPOSA study) in October 2020.

Based mainly on the results from the MARIPOSA study, US and EU applications for Ami and Laz for Ami/Laz for the treatment of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC were submitted in December 2023. In the US, Ami and Laz were approved for the indications presented in the table below in August 2024. The EU application is under review. As of November 2024, Ami/Laz for the treatment of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC has been approved in the US only.

Ami	RYBREVANT, in combination with lazertinib, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.
Laz	LAZCLUZE, in combination with amivantamab, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

In Japan, the applicant initiated patient enrollment in a global phase I study (Study NSC1001) and the MARIPOSA study in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC in September 2019 and December 2020, respectively.

The applicant has now filed a partial change application for Ami and a marketing application for Laz for Ami/Laz for the treatment of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, based mainly on the results from the MARIPOSA study.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Ami

Since the present application is intended for a new indication and a new dosage, no quality data have been submitted.

2.2 Laz

2.2.1 Drug substance

2.2.1.1 Characterization

The drug substance is a white to slightly yellow-brown powder, and its appearance, melting point, solubility, acid dissociation constant, partition coefficient, hygroscopicity, and particle size were determined. Although 7 polymorphic forms of the drug substance ([redacted], [redacted], and [redacted]) have been identified, [redacted] only is produced by the proposed commercial synthesis process and has been demonstrated to be stable at room temperature.

Its chemical structure has been elucidated by mass spectrometry (MS), elemental analysis, infrared absorption spectroscopy (IR), ultraviolet spectroscopy (UV), and nuclear magnetic resonance spectrometry (NMR) (^{1}H-NMR, ^{13}C-NMR).

2.2.1.2 Manufacturing process

The drug substance is synthesized using Starting Material A[3)] and Starting Material B.[4)] [redacted] synthesis methods ([redacted]) are in place for manufacturing the drug substance. Batch analysis data and the results of stability studies demonstrated the comparability of quality attributes between the drug substances manufactured by these synthesis methods.

A quality control strategy was developed based on the following etc. (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) and determination of the proven acceptable ranges (PARs) for manufacturing process parameters through quality risk assessment

Table 1. Overview of drug substance control strategy

CQA	Method of control
Appearance	Specification
Identification	Specification
Content	[redacted], Specification
Related substances	[redacted], Specification
Residual solvents	[redacted], Specification
Inorganic impurities	Specification
[redacted]	[redacted]
Water content	[redacted], Specification
Particle size distribution	[redacted], Specification

3) [redacted]
4) [redacted]

Steps Intermediate A[5)] [redacted], Intermediate B[6)] [redacted] ([redacted] only), [redacted], and [redacted] have been defined as critical steps. As a critical intermediate, [redacted] is controlled.

2.2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identification (IR), purity (related substances [liquid chromatography (LC)], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size, and assay (LC).

[redacted] was added in the drug substance specification in the course of regulatory review.

2.2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	Double low-density polyethylene bags + paper drum	36 months
Accelerated		40°C	75%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when packaged in double low-density polyethylene bags and stored at room temperature, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E guideline. The long-term testing will be continued up to [redacted] months.

2.2.2 Drug product

2.2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet containing 96.48 mg or 289.44 mg of lazertinib mesilate hydrate (equivalent to 80 mg or 240 mg, respectively, of lazertinib) and the following excipients: hydrophobic colloidal silica, microcrystalline cellulose, D-mannitol, croscarmellose sodium, magnesium stearate, [redacted] (the 80 mg tablet only), and [redacted] (the 240 mg tablet only).

2.2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: [redacted], [redacted], [redacted], [redacted], [redacted], tablet compression, preparation of coating solution, film coating, and packaging/testing/storage. [redacted] operate in a batch mode, and unit operations up to [redacted] are performed in a continuous manufacturing mode.

A quality control strategy was developed based on the following considerations (Table 3).

- Identification of CQAs

[redacted]

- Identification of CPPs and critical material attributes and determination of PARs for manufacturing process parameters through quality risk assessment
- Use of real time release testing (RTRT) for [redacted]

Table 3. Overview of drug product control strategy

CQA	Method of control
Appearance	[redacted], Specification
Identification	Specification
Strength	[redacted], Specification
Purity	Specification
Uniformity of dosage units	[redacted], Specification
Dissolution	[redacted], Specification
[redacted]	[redacted]

*[redacted]

[redacted] have been defined as critical steps, and process control items and values have been established for the following steps: [redacted].

2.2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (near infrared spectroscopy [NIR] or LC/UV[7)]), purity (degradation products [LC]), uniformity of dosage units (NIR or LC[8)]), dissolution (LC), and assay (NIR or LC[8)]). RTRT ([redacted] tested by NIR, LC/UV,[7)] or LC[8)]) performed as in-process testing is used for [redacted] to make release decisions of the drug product.

2.2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. [redacted] drug product failed to meet the specification for [redacted] at [redacted] time point under the accelerated condition, but was stable under the long-term and intermediate conditions. Photostability testing showed that the drug product is photostable.

Table 4. Stability studies on drug product*

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	Blister packs (polyvinyl chloride-polychlorotrifluoroethylene film and aluminum foil)	24 months
Intermediate		30°C	75%RH		24 months
Accelerated		40°C	75%RH		6 months

* For [redacted] of [redacted] drug product, a method different from the proposed method was used in [redacted] study up to [redacted], [redacted] study up to [redacted], and [redacted] study. The discriminatory power of the both methods has been demonstrated for [redacted].

Based on the above, a shelf-life of 24 months has been proposed for the drug product when packaged in blister packs (polyvinyl chloride-polychlorotrifluoroethylene film and aluminum foil) and stored at room temperature. The long-term testing will be continued up to [redacted] months.

[7)] If identification cannot be tested appropriately by NIR, LC/UV should be used.
[8)] If uniformity of dosage units and assay cannot be tested appropriately by NIR, LC should be used.

2.2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations etc., PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.2.R.1 Batch definition in a continuous manufacturing process for the drug product

The applicant's explanation about the batch definition in a continuous manufacturing process (steps [redacted]) for the drug product:

The size of a batch is defined by [redacted] and [redacted]. As the target [redacted] for the continuous process during commercial production has been defined for control, the commercial batch size varies depending on [redacted]. Based on the manufacturing history, [redacted] had no impact on process performance and product quality. Thus, [redacted] is listed as an item subject to minor change notification in the application form.

PMDA considers that the batch size in the continuous manufacturing process requires appropriate change control. Since [redacted] is not established in the present application, PMDA cannot conclude that when [redacted] increases, the risk to process performance and product quality is small. Given these points, PMDA requested the applicant to list [redacted] as an item subject to partial change application in the application form. The applicant responded to the request.

2.2.R.2 Control of the strength of the drug product

The applicant's explanation about the control of the strength of the drug product:

In a continuous manufacturing process, 2 diversion points are located at [redacted] and [redacted] to allow diversion of core tablets potentially not conforming to the specification for the content of the drug substance. In [redacted], (1) an analytical model based on the results of analysis of [redacted] by [redacted] and (2) a process model[9)] based on [redacted] data on [redacted] and [redacted] of [redacted] to be used are used to predict the drug substance content of core tablets. Based on the results of this prediction, core tablets potentially not meeting the in-process acceptance criteria for the content of the drug substance[10)] are diverted. In [redacted], core tablets are sampled from the tablet press outlet at [redacted] for in-process testing including [redacted], and core tablets not meeting the acceptance criteria and all core tablets collected in [redacted] are diverted. The above results of in-process testing are used also for RTRT proposed to make release decisions of the drug product.

PMDA considers that the control strategy policy proposed by the applicant is acceptable, but requested the applicant to include [redacted] by models in this policy in the application form. The applicant responded to the request.

[9)] This is a tool independent of the model (1), and is used to detect and divert core tablets potentially not meeting the in-process acceptance criteria for the content of the drug substance and to [redacted].

[10)] Taking account of [redacted], [redacted] by models was established to ensure that the drug substance content of core tablets is within the limits of [redacted]% to [redacted]%.

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

3.1 Ami

Although the present application is intended for a new indication and a new dosage, no new study data have been submitted because the non-clinical pharmacology data on Ami monotherapy were previously evaluated for the initial approval of Ami. The data from non-clinical pharmacology studies of Ami/Laz were submitted as non-clinical pharmacology data on Laz [see Section 3.2].

3.2 Laz

In this section, unless otherwise specified, the doses and concentrations of Laz are expressed as free base.

3.2.1 Primary pharmacodynamics

3.2.1.1 Inhibition of phosphorylation of EGFR kinases etc.

3.2.1.1.1 *In vitro* (CTD 4.2.1.1.1, 4.2.1.1.2)

Inhibition of the phosphorylation of wild-type and mutant human EGFR (recombinant proteins) by Laz, osimertinib mesylate (Osi), AZ5104 (a metabolite of Osi), afatinib, and erlotinib was determined by fluorescence resonance energy transfer (FRET). The IC_{50} values of these drugs are shown in Table 5.

Table 5. Inhibition of EGFR phosphorylation by Laz and other substances

EGFR	IC_{50} value (nmol/L)				
	Laz	Osi	AZ5104	Afatinib	Erlotinib
Wild type	25.2	16.7	2.5	0.2	0.6
Ex19del	5.3	8.6	2.2	0.2	0.8
L858R	20.6	12.2	4.2	0.3	0.9
L858R/T790M	3.7	4.5	2.4	18.6	549.3
T790M	1.7	2.2	0.7	1.6	395.2
Ex19del/T790M	3.5	3.3	1.2	7	715.6

n = 1

Inhibition of the phosphorylation of the ErbB family members, human HER2 and HER4, and EGFR L858R/T790M (a recombinant protein) by Laz, Osi, AZ5104, and afatinib was determined by FRET. The IC_{50} values of these drugs are shown in Table 6.

Table 6. Inhibition of phosphorylation of HER2 and HER4 by Laz and other substances

Kinase	IC_{50} value (nmol/L)			
	Laz	Osi	AZ5104	Afatinib
HER2	1,017	78.6	44.7	46.8
HER4	363.1	30.2	3.1	9.5
$EGFR^{L858R/T790M}$	3.7	4.5	2.4	18.6

n = 1

Using H2073 human NSCLC cell line expressing wild-type EGFR, PC9 human NSCLC cell line expressing EGFR Ex19del, and H1975 human NSCLC cell line expressing EGFR L858R/T790M, inhibition of EGFR phosphorylation by Laz, Osi, AZ5104, afatinib, and erlotinib was determined by Western blotting. The IC_{50} values of these drugs are shown in Table 7.

Table 7. Inhibition of EGFR phosphorylation in human NSCLC cell lines by Laz and other substances

Cell line	EGFR	IC_{50} value (nmol/L)				
		Laz	Osi	AZ5104	Afatinib	Erlotinib
H2073	Wild type	318.1	244.4	16.7	6.4	>1,000
PC9	Ex19del	2.7	4.8	2.3	2.3	15.7
H1975	L858R/T790M	3.6	11.2	<1	6.9	>1,000

n = 1

Inhibition of the phosphorylation activity of 304 kinases by Laz was determined by homogeneous time-resolved fluorescence (HTRF) or radiometry. Laz 1 μmol/L inhibited the phosphorylation activity of the following kinases by ≥50%, and the percent inhibition of phosphorylation[11)] and the IC_{50} values for these kinases are shown in Table 8.

Table 8. Inhibition of phosphorylation activity of various kinases by Laz

Kinase	% Inhibition (%)	IC_{50} value (nmol/L)	Kinase	% inhibition (%)	IC_{50} value (nmol/L)
Axl	67	523	MARK1	99	>100,000
Wild type EGFR	86	76	Mer	71	225
$EGFR^{L858R}$	91	—	MLK1	97	17, 31
$EGFR^{L861Q*1}$	86	—	RET	86	419, 473
$EGFR^{T790M}$	101	—	$RET^{V804L*2}$	96	—
$EGFR^{L858R/T790M}$	98	2	$Ret^{V804M*3}$	82	—
Fer	85	118, 154	RIPK2	53	155
JAK3	50	917	Rsk3	59	575

n = 1 or 2 (individual values); —, Not determined; *1 Leucine at position 861 in EGFR substituted with glutamine;
*2 Valine at position 804 in RET substituted with leucine; *3 Valine at position 804 in RET substituted with methionine

3.2.1.1.2 *In vivo* (CTD 4.2.1.1.9)

Nude mice implanted subcutaneously with the H1975 cell line (9/group) were dosed orally with Laz (3 or 10 mg/kg) quaque die or once daily (QD) for 3 days, and inhibition of the phosphorylation of EGFR etc. in tumor tissue by Laz was determined by Western blotting. At 2 and 24 hours after the last dose, Laz inhibited the phosphorylation of EGFR and the downstream signaling proteins AKT and ERK1/2.

3.2.1.2 Induction of apoptosis (CTD 4.2.1.1.1)

Using the PC9 cell line and the H1975 cell line, the apoptotic effects of Laz, Osi, afatinib, and erlotinib were determined by measuring caspase 3/7 activity. The EC_{50} values of these drugs are shown in Table 9.

Table 9. Induction of apoptosis by Laz and other substances in human NSCLC cell lines expressing mutant EGFR

Cell line	EGFR	EC_{50} value (nmol/L)			
		Laz	Osi	Afatinib	Erlotinib
PC9	Ex19del	14.7	31.7	2.3	35.6
H1975	L858R/T790M	38.8	94.9	370.2	23,880.0

n = 1

11) Percent inhibition of phosphorylation (%) ={1 − (kinase activity in the presence of Laz)/(kinase activity in the absence of Laz)}× 100

3.2.1.3 Growth inhibition of cancer cell lines

3.2.1.3.1 *In vitro* (CTD 4.2.1.1.1)

Inhibition of the proliferation of the H2073, PC9, and H1975 cell lines by Laz, Osi, AZ5104, afatinib, and erlotinib was evaluated based on the amount of ATP from viable cells. The half-maximal growth inhibitory concentrations (GI_{50}) of these drugs are shown in Table 10.

Table 10. Anti-cancer activities of Laz and other substances against human NSCLC cell lines expressing EGFR

Cell line	EGFR	GI_{50} value (nmol/L)				
		Laz	Osi	AZ5104	Afatinib	Erlotinib
H2073	Wild type	711.1	437.7	23.8	41.4	609.7
PC9	Ex19del	4.7	8.5	2.3	2.3	9.9
H1975	L858R/T790M	6.3	10.1	2.5	6.9	13,790.0

n = 1

3.2.1.3.2 *In vivo*

3.2.1.3.2.1 NSCLC cell lines

3.2.1.3.2.1.1 Laz monotherapy (CTD 4.2.1.1.4, 4.2.1.1.6, 4.2.1.1.11)

The anti-tumor activities of Laz and Osi were investigated in nude mice implanted subcutaneously with the PC9 cell line (10/group). The day of implantation was designated as Study Day 0. When the mean tumor volume reached 138 mm^3 (Day 5), mice began receiving Laz (0.3, 1, or 3 mg/kg) or Osi (3 mg/kg) QD orally for 25 days, and tumor volumes were calculated. Treatment with either Laz or Osi statistically significantly inhibited tumor growth compared with vehicle control (50 mmol/L citric acid and 0.5% methylcellulose solution) (Figure 1).

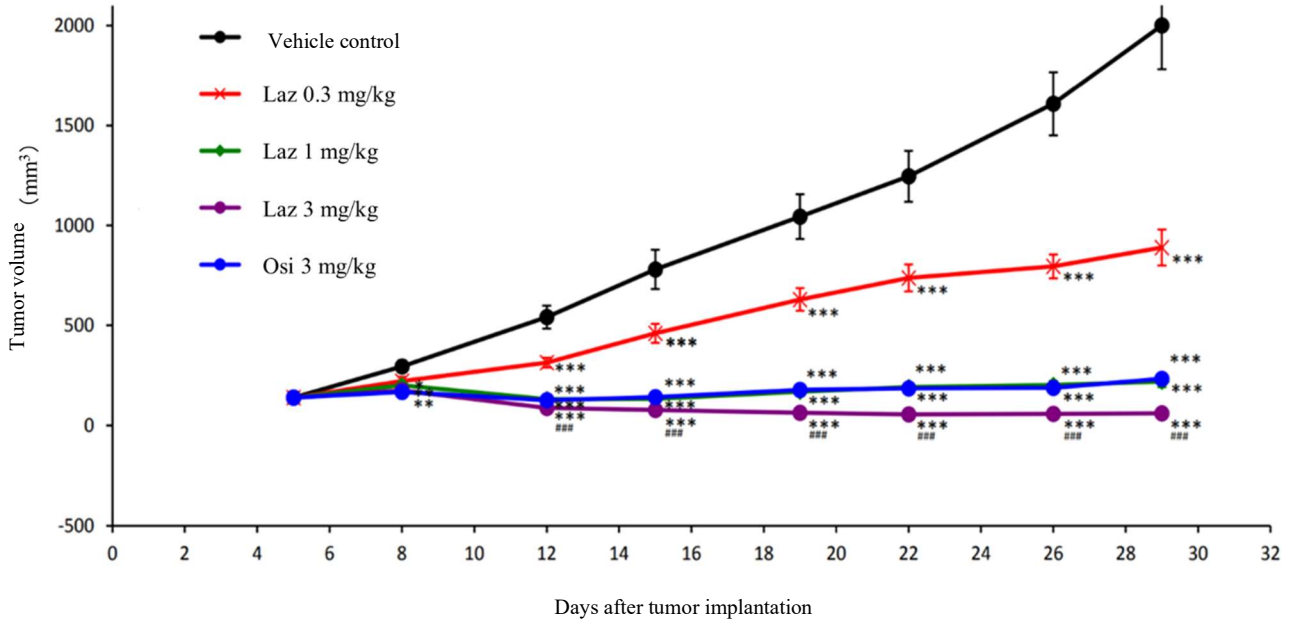

Figure 1. Anti-tumor activities of Laz and Osi in nude mice implanted subcutaneously with PC9 cell line
n = 10, Mean ± SD, *$P < 0.05$ vs. vehicle control (Dunnett's multiple comparison test),
**$P < 0.01$ vs. vehicle control (Dunnett's multiple comparison test),
***$P < 0.001$ vs. vehicle control (Dunnett's multiple comparison test), ###$P < 0.001$ vs. Osi (t-test)

The anti-tumor activity of Laz was investigated in nude mice implanted subcutaneously with the H1975 cell line (6 or 12/group). When the mean tumor volume reached approximately 200 mm^3, mice began receiving

Laz (1, 3, or 10 mg/kg) QD or Laz (3 mg/kg) BID orally, and tumor volumes were calculated on Treatment Day 13.[12)] Treatment with Laz statistically significantly inhibited tumor growth compared with vehicle control (5% N-methylpyrrolidone [NMP] solution) ($P < 0.01$, t-test).

The anti-tumor activities of Laz and Osi were investigated in nude mice implanted subcutaneously and intracranially with luciferase-transfected H1975 cell line (7/group). The day of implantation was designated as Study Day 0. Beginning at Day 13, mice received Laz (1, 3, or 10 mg/kg) or Osi (1, 3, or 10 mg/kg) QD orally. On Day 21, tumor volumes in subcutaneous tissues and intracranial bioluminescence were measured. Treatment with either Laz or Osi statistically significantly inhibited both subcutaneous and intracranial tumor growth compared with vehicle control (50 mmol/L citric acid and 0.5% methylcellulose solution) ($P < 0.05$, Dunnett's multiple comparison test).

3.2.1.3.2.1.2 Ami/Laz (CTD 4.2.1.1.17)

The anti-tumor activities of Laz and Ami monotherapies or Laz in combination with Ami were investigated in nude mice implanted subcutaneously with the H1975 cell line (10/group). The day of implantation was designated as Study Day 0. On Day 15, mice began receiving Laz (10 mg/kg QD orally) or Ami (10 mg/kg twice weekly intraperitoneally) alone or Laz in combination with Ami for 21 days, and tumor volumes were calculated. On Day 29, Laz, Ami, and Ami/Laz statistically significantly inhibited tumor growth compared with vehicle control (0.5% methylcellulose solution) (Laz, $P < 0.0001$; Ami, $P = 0.0003$; Ami/Laz, $P < 0.0001$; Dunnett's multiple comparison test). Ami/Laz showed statistically significantly increased anti-tumor activity compared with Ami (Figure 2, $P < 0.0001$, Dunnett's multiple comparison test).

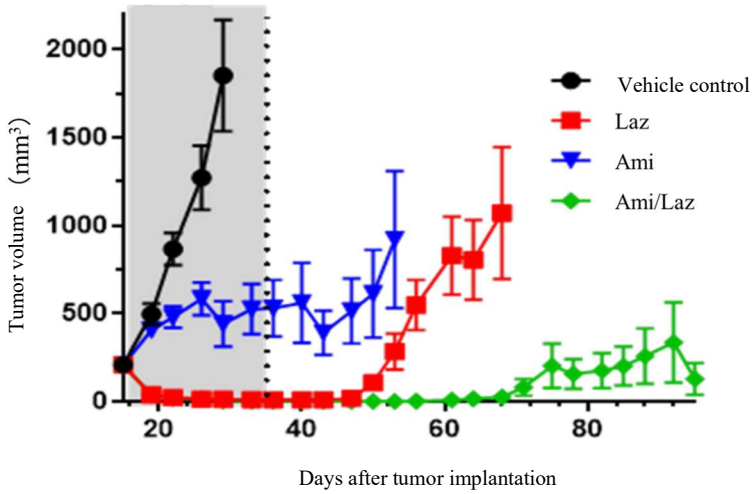

Figure 2. Anti-tumor activities of Laz and Ami monotherapies and Ami/Laz in nude mice implanted subcutaneously with H1975 cell line
n = 10, Mean ± SD, Dosing period denoted by gray shading

Using nude mice implanted subcutaneously with the H1975 cell line overexpressing hepatocyte growth factor (HGF) (10/group), the anti-tumor activities of Laz and Ami monotherapies or Laz in combination with Ami in

[12)] Owing to error of drug preparation on Day 11 onwards in the 1 mg/kg QD group, tumor volumes calculated on Day 10 were used.

an EGFR-TKI-resistant model[13] were investigated. The day of implantation was designated as Study Day 0. On Day 10, mice began receiving Laz (10 mg/kg QD orally) or Ami (10 mg/kg twice weekly intraperitoneally) alone or Laz in combination with Ami for 21 days, and tumor volumes were calculated. On Day 28, Laz, Ami, and Ami/Laz statistically significantly inhibited tumor growth compared with vehicle control (0.5% methylcellulose solution) (Laz, $P = 0.0030$; Ami, $P = 0.0059$; Ami/Laz, $P < 0.0001$; Dunnett's multiple comparison test). Ami/Laz showed statistically significantly increased anti-tumor activity compared with Laz or Ami alone (Figure 3, $P < 0.0001$ for both, Dunnett's multiple comparison test).

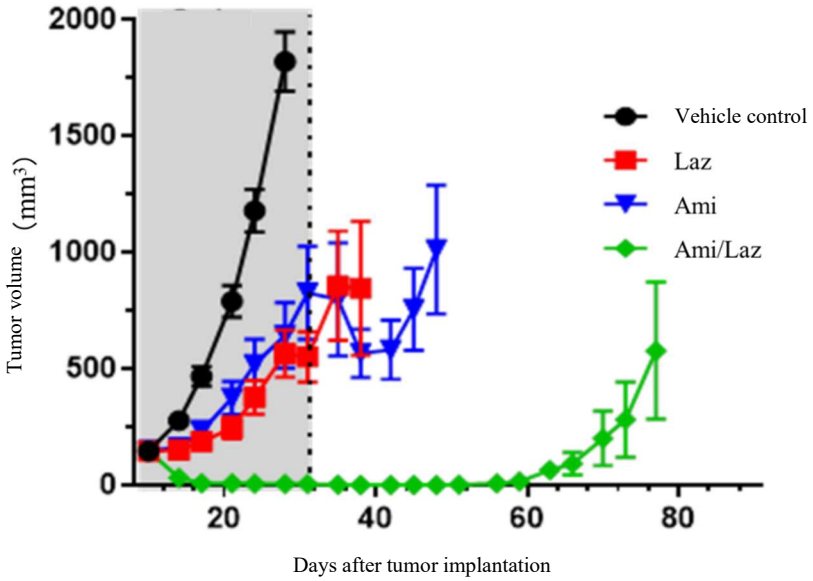

Figure 3. Anti-tumor activities of Laz and Ami monotherapies and Ami/Laz in nude mice implanted subcutaneously with H1975 cell line overexpressing HGF
n = 10, Mean ± SD, Dosing period denoted by gray shading

3.2.1.3.2.2 Non-NSCLC cancer cell lines (CTD 4.2.1.1.5, 4.2.1.1.10)

The anti-tumor activities of Laz and Osi were investigated in nude mice implanted subcutaneously with (1) murine pro-B cell-derived Ba/F3 cell line expressing EGFR L858R or (2) human skin squamous carcinoma A431 cell line expressing wild-type EGFR [(1) 8/group and (2) 7/group]. The results are shown below.

(1) When the mean tumor volume reached 160 mm^3, mice began receiving Laz (1, 3, or 10 mg/kg) or Osi (1, 3, or 10 mg/kg) QD orally for 11 days. Treatment with either Laz or Osi statistically significantly inhibited tumor growth compared with vehicle control (0.5% methylcellulose solution) ($P < 0.01$, Dunnett's multiple comparison test). Laz 1 mg/kg showed statistically significantly increased anti-tumor activity compared with Osi 1 mg/kg ($P < 0.01$, t-test).

(2) At 27 days post-implantation, mice began receiving Laz (1, 3, or 10 mg/kg) or Osi (1, 3, or 10 mg/kg) QD orally for 19 days. Tumor growth inhibition (TGI)[14] was 9.9%, 51.4%, and 83.7% in the Laz 1, 3, and 10 mg/kg groups, respectively, and −18.2%, 72.6%, and 101.3% in the Osi 1, 3, and 10 mg/kg groups, respectively.

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[13] HGF is the ligand of MET, and activation of the MET signaling pathway has been reported as an acquired resistance mechanism to EGFR-TKIs (*Br J Cancer*. 2019; 121: 725-37).

[14] TGI (%) = {1− (Change in mean tumor volume in the Laz or Osi group)/(Change in mean tumor volume in the vehicle control [0.5% methylcellulose solution] group)} × 100

3.2.2 Secondary pharmacodynamics

3.2.2.1 Effects on various receptors, transporters, and ion channels (CTD 4.2.1.2.1)

The effects of Laz on 80 receptors, transporters, and ion channels were investigated using radioligands. Laz 1 μmol/L caused ≥50% inhibition of the $5HT_{2B}$ receptor and the 5-HT transporter, and the IC_{50} values of Laz were 180 and 40 nmol/L, respectively.

Using rat brain synaptosomes and the radiolabeled 5-HT, the effect of Laz on the uptake of 5-HT was evaluated. The IC_{50} value of Laz for the inhibition of 5-HT uptake was 110 nmol/L.

The applicant's explanation about the above findings:
Given that the unbound plasma C_{max} of Laz at the recommended clinical dose of 240 mg QD was 8.2 nmol/L,[15] inhibition of the above receptor etc. by Laz is unlikely to cause a safety problem in the clinical use of Laz.

3.2.3 Safety pharmacology

3.2.3.1 Effects on central nervous system (CTD 4.2.1.3.5)

Following a single oral dose of Laz (25, 50, or 100 mg/kg) in rats (8/group), the effects of Laz on the central nervous system were assessed by modified Irwin's test. There were no Laz-related effects.

3.2.3.2 Effects on cardiovascular system

3.2.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3.1)

Using a CHO cell line transfected with hERG, the effect of Laz on hERG potassium current was investigated. Laz at 1.0, 2.5, 4.8, and 9.3 μmol/L inhibited the hERG potassium current by 25.5 ± 0.5%, 31.3 ± 1.6%, 59.8 ± 2.1%, and 53.2 ± 1.3%, respectively (n = 3, mean ± standard error [SE]). The IC_{50} value was 5.3 ± 2.0 μmol/L.

3.2.3.2.2 Effects on heart rate, blood pressure, and ECG (CTD 4.2.1.3.2 [non-GLP study], 4.2.1.3.3)

Following a single oral dose of Laz (5, 10, or 20 mg/kg) in dogs (n = 4), the effects of Laz on heart rate, blood pressure, and ECG (PR, QT, and QTc intervals, QRS duration) were investigated. Laz 20 mg/kg mildly lowered heart rate (−19%).

The applicant's explanation about the above finding:
Given that the unbound plasma C_{max} of Laz at 20 mg/kg in dogs (8.3 ng/mL) was higher than the unbound plasma C_{max} of Laz at the recommended clinical dose of 240 mg QD (4.54 ng/mL),[15] the above finding is unlikely to become a safety problem in the clinical use of Laz.

Using the isolated rabbit heart (n = 4), the effects of Laz 1, 3, 10, and 30 μmol/L on ECG (QT interval, QRS duration, QT_{peak} interval, T_{peak}-T_{end} duration, the appearance of early after depolarizations) and the monophasic action potential duration at 30%, 50%, and 90% repolarization were investigated. Laz 30 μmol/L prolonged T_{peak}-T_{end}.

[15] Calculated based on the C_{max} (568 ng/mL) on Day 22 following administration of Laz 240 mg QD in Japanese patients with NSCLC in Study NSC1001 [see Section 6.2.2.1.2] and plasma protein binding in humans (99.2%) [see Section 4.2.2.2].

The applicant's explanation about the above finding:
Given that the unbound plasma C_{max} of Laz at the recommended clinical dose of 240 mg QD was 8.2 nmol/L,[15] the above finding is unlikely to become a safety problem in the clinical use of Laz.

3.2.3.3 Effects on respiratory system (CTD 4.2.1.3.4)

Following a single oral dose of Laz (25, 50, 79, or 100 mg/kg) in rats (8/group), the effects of Laz on respiratory rate, tidal volume, and minute volume were investigated. Administration of Laz 79 and 100 mg/kg resulted in decreases in mean tidal volume and minute volume.

The applicant's explanation about the above findings:
Given that the unbound plasma C_{max} of Laz at 50 mg/kg in rats (8.33 ng/mL) was higher than the unbound plasma C_{max} of Laz at the recommended clinical dose of 240 mg QD (4.54 ng/mL),[15] the above findings are unlikely to become a safety problem in the clinical use of Laz.

3.2.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of Laz is acceptable.

3.2.R.1 Mechanism of action of Laz and efficacy of Laz and Ami/Laz

The applicant's explanation about the mechanism of action of Laz and its efficacy in the treatment of *EGFR* mutation-positive NSCLC:
Activating mutations (Ex19del and L858R) account for approximately 90% of all *EGFR* mutations in NSCLC (Clinical Practice Guideline for Lung Cancer 2023). The EGFR T790M mutation has been reported as an acquired resistance mechanism to the existing EGFR-TKIs, gefitinib and erlotinib (*Transl Lung Cancer Res*. 2019; 8: S247-64), and 50% to 60% of patients with EGFR-TKI-resistant NSCLC had the T790M mutation (*J Thorac Oncol*. 2016; 11: 2022-6, *Clin Cancer Res*. 2013; 19: 2240-7, etc.).

Laz is considered to inhibit tumor growth of *EGFR* mutation-positive NSCLC by binding to the intracellular kinase domain of Ex19del, L858R, or T790M *EGFR* mutants (*Clin Cancer Res*. 2019; 25: 2575-87) and inhibiting EGFR phosphorylation and downstream signaling pathways [see Section 3.2.1.1].

Taking account of the above mechanism of action, and given that Laz inhibited tumor growth in nude mice implanted subcutaneously with human NSCLC cell lines with Ex19del or L858R/T790M mutations [see Section 3.2.1.3.2.1.1], the efficacy of Laz is expected in the treatment of NSCLC with *EGFR* mutations including T790M.

The applicant's explanation about the efficacy of Ami/Laz in the treatment of *EGFR* mutation-positive NSCLC: Given that Ami/Laz showed higher anti-tumor activity than Ami or Laz alone [see Section 3.2.1.3.2.1.2], and taking account of the following points etc., Ami/Laz is expected to have superior efficacy than Ami or Laz alone.

- As shown below, Laz and Ami have distinct mechanisms of inhibiting tumor growth.
  - Laz inhibits tumor growth by binding to the intracellular kinase domain of EGFR and inhibiting signaling.
  - Ami inhibits tumor growth by binding to the extracellular domains of EGFR and MET, inhibiting signaling, inducing ADCC activity, etc. (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024").
- Activation of MET-mediated signaling has been reported as an acquired resistance mechanism to Laz (*Br J Cancer*. 2019; 121: 725-37). Ami may suppress acquired resistance to Laz by inhibiting MET signaling.

In addition, the applicant's explanation about differences in pharmacological properties between Laz and the existing EGFR-TKIs (gefitinib, erlotinib, afatinib, dacomitinib, Osi):
The pharmacological properties of Laz and the existing EGFR-TKIs are shown below.

- All of Laz, afatinib, dacomitinib, and Osi inhibit the phosphorylation of EGFR T790M (see Section 3.2.1.1.1, *Cancer Discov*. 2014; 4: 1046-61).
- Gefitinib, erlotinib, afatinib, and dacomitinib have been reported to exhibit lower potency against EGFR mutants than wild-type EGFR and lower potency against EGFR L858R/T790M and Ex19del/T790M than EGFR Ex19del and L858R (*Cancer Discov*. 2014; 4: 1046-61). On the other hand, Laz and Osi exhibited greater potency against EGFR mutants than wild-type EGFR and tended to show greater potency against EGFR L858R/T790M and Ex19del/T790M than EGFR Ex19del and L858R [see Section 3.2.1.1.1].
- Laz, afatinib, and Osi inhibited the phosphorylation of HER2 and HER4, in addition to EGFR phosphorylation, whereas Laz tended to have less activity against phosphorylation of HER2 and HER4, compared with afatinib and Osi [see Section 3.2.1.1.1].

PMDA's view:
PMDA largely accepted the applicant's explanation. However, the significance of Ami binding to both EGFR and MET when Ami/Laz inhibits tumor growth of *EGFR* mutation-positive NSCLC is not fully understood at present. Thus, information collection should be continued, and if a new finding becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

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

4.1 Ami

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of Ami, and no new study data have been submitted.

4.2 Laz

In this section, unless otherwise specified, the doses and concentrations of Laz are expressed as free base.

The non-clinical PK of Laz were studied in dogs etc. Studies on the plasma protein binding, drug metabolizing enzymes, transporters, etc. of Laz were conducted using human or animal biomaterials.

Laz concentrations in dog plasma were determined using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (Lower limit of quantitation [LLOQ], 1 or 10 ng/mL[16)]). The tissue distribution of radioactivity in rats was determined by quantitative whole-body autoradiography (LLOQ, 27.4 or 127.9 ng Eq./g[17)]).

4.2.1 Absorption

4.2.1.1 Single-dose studies

Following a single intravenous administration of Laz 0.3, 1, or 3 mg/kg or a single oral administration of Laz 0.3, 1, 3, or 10 mg/kg in male dogs, plasma concentrations of Laz were determined (Table 11). Laz exposure increased in an approximately dose-proportional manner over the dose range tested. The oral bioavailability (BA) of Laz was 57.8% to 77.7%.

Table 11. PK parameters of Laz (male dogs, single IV or oral administration)

Route of administration	Dose (mg/kg)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)	BA (%)
IV	0.3	3	—	—	580 ± 27.8	7.2 ± 2.0	518 ± 25.0	3,710 ± 718	—
	1	4	—	—	2,301 ± 279	7.2 ± 1.1	440 ± 54.3	2,861 ± 453	—
	3	4	—	—	6,951 ± 1,925	7.4 ± 0.7	453 ± 102	2,931 ± 459	—
Oral	0.3	4	67.0 ± 28.1	1.0 (0.5, 1.0)	341 ± 48.7	8.3 ± 1.7	—	—	57.8
	1	4	311 ± 29.6	1.0 (1.0, 2.0)	1,941 ± 410	11.0 ± 1.1	—	—	77.7
	3	4	835 ± 175	1.0 (1.0, 2.0)	5,498 ± 1,440	10.1 ± 4.0	—	—	73.2
	10	4	2,387 ± 558	1.5 (1.0, 2.0)	15,714 ± 2,449	8.4 ± 4.1	—	—	64.5

Mean ± SD; —, Not calculated; *Median (Min., Max.)

Following a single oral administration of Laz 30 mg/kg in male and female dogs, plasma concentrations of Laz were determined (Table 12). There were no clear sex differences in the PK of Laz.

Table 12. PK parameters of Laz (male and female dogs, single oral administration)

Sex	C_{max} (ng/mL)	t_{max}* (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
M	7,356 ± 1,623	1.0 (0.5, 4.0)	70,985 ± 15,343	11.5 ± 1.8
F	8,852 ± 1,266	2.0 (0.5, 2.0)	67,526 ± 13,902	13.0 ± 1.9

Mean ± SD; n = 3; *Median (Min., Max.)

4.2.1.2 Repeated-dose studies

Following oral QD dosing of Laz 2, 4, or 8 mg/kg for 13 weeks in male and female dogs, plasma concentrations of Laz were determined (Table 13). Laz exposure increased in an approximately dose-proportional manner over the dose range tested. There were no clear sex differences in the PK of Laz.

16) The LLOQs were 1 ng/mL in single intravenous and oral dose studies and 10 ng/mL in repeated oral dose studies.
17) The LLOQs were 27.4 ng Eq./g at sampling time points of 8, 12, 24, 48, 72, 120, and 336 hours after dosing of Laz and 127.9 ng Eq./g at sampling time points of 1, 2, 4, 6, and 168 hours post-dose.

Table 13. PK parameters of Laz (male and female dogs, 13-week oral administration)

Sampling day (Day)	Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)
1	2	M	3	540 ± 46.5	1.00 (1.00, 1.00)	2,960 ± 112
		F	3	376 ± 102	1.00 (1.00, 1.00)	2,180 ± 273
	4	M	3	654 ± 460	1.00 (1.00, 4.00)	4,610 ± 2,220
		F	3	625 ± 96.1	1.00 (1.00, 1.00)	4,310 ± 371
	8	M	5	1,350 ± 364	1.00 (1.00, 1.10)	10,300 ± 1,630
		F	5	805 ± 207	1.00 (1.00, 4.00)	9,330 ± 1,620
85	2	M	3	280 ± 23.4	1.00 (1.00, 1.00)	3,380 ± 837
		F	3	219 ± 29.6	2.00 (2.00, 2.00)	2,400 ± 434
	4	M	3	520 ± 172	1.00 (1.00, 1.00)	5,780 ± 1,720
		F	3	520 ± 56.6	1.00 (1.00, 2.00)	5,500 ± 1,020
	8	M	4	975 ± 176	2.00 (1.00, 4.00)	14,600 ± 2,080
		F	4	897 ± 257	1.50 (1.00, 2.00)	11,700 ± 1,180

Mean ± SD, * Median (Min., Max.)

4.2.1.3 *In vitro* membrane permeability

The membrane permeability of Laz was evaluated in the human colon carcinoma Caco-2 cell line. The apparent permeability coefficient in the apical to basolateral direction ($P_{app\ A\rightarrow B}$) of Laz 10 μmol/L was 2.90×10^{-6} cm/sec.

The applicant's explanation:

Given the above results and the $P_{app\ A\rightarrow B}$ values of poorly permeable atenolol and highly permeable phenytoin (0.53×10^{-6} and 32.04×10^{-6} cm/sec, respectively), Laz has moderate permeability.

4.2.2 Distribution

4.2.2.1 Tissue distribution

Following a single oral dose of ^{14}C-Laz 10 mg/kg in male pigmented rats, the tissue distribution of radioactivity was determined. Extensive tissue distribution of radioactivity was observed, and maximum concentrations of radioactivity were reached by 8 hours post-dose in most tissues including blood. The maximum concentrations of radioactivity in the uveal tract, stomach, small intestine, liver, Harderian gland, lung, eye, spleen, bone marrow (femur), thyroid gland, adrenal gland, kidney (cortex), kidney, pituitary gland, fat, kidney (medulla), pigmented skin, and unpigmented skin (116,000,[18] 102,000,[19] 47,000, 39,900, 39,400, 26,800, 18,200, 17,700, 16,200, 15,700, 15,500, 14,000, 13,400, 11,600, 11,500, 10,500, 8,110, and 4,000 ng Eq./g, respectively) were particularly higher than the maximum concentration of radioactivity in blood (526 ng Eq./g). Even at 336 hours post-dose, radioactivity was detected in most tissues, and the tissue radioactivity concentration was particularly higher in the uveal tract (40,819 ng Eq./g) than in other tissues.

[18] Since the radioactivity concentrations in the uveal tract at 6, 8, 24, and 72 hours after dosing of ^{14}C-Laz were above the upper limit of quantitation, the radioactivity concentrations at these time points were set to the upper limit of quantitation.

[19] Since the radioactivity concentration in the stomach at 1 hour after dosing of ^{14}C-Laz was above the upper limit of quantitation, the radioactivity concentration at this time point was set to the upper limit of quantitation.

The applicant explained that the above results indicated melanin-binding of both or either of Laz and its metabolites. The safety of Laz in the skin and eyes is described in Sections "7.R.3.6 Skin disorders (including paronychia)" and "7.R.3.10 Eye disorders."

4.2.2.2 Plasma protein binding

The plasma from mouse, rat, dog, monkey, or human was incubated with Laz (1-10 μmol/L) at 37°C for 4 hours, and the plasma protein binding of Laz was determined using an equilibrium dialysis method. The plasma protein binding of Laz was 99.1% to 99.7%, 99.0% to 99.6%, 99.5% to 99.8%, 98.4% to 99.6%, and 99.1% to 99.7%, respectively.

Human serum albumin (43 mg/mL) or human α1-acid glycoprotein (0.5-2 mg/mL) was incubated with Laz (0.3-3 μmol/L) at 37°C for 6 hours, and the binding of Laz to human serum albumin and to human α1-acid glycoprotein was determined using an equilibrium dialysis method. The binding of Laz to (1) human serum albumin and to human α1-acid glycoprotein [(2) 0.5, (3) 1, and (4) 2 mg/mL] was (1) 94.1% to 94.9%, (2) 72.0% to 74.0%, (3) 83.0% to 86.0%, and (4) 91.9% to 92.5%.

4.2.2.3 Distribution in blood cells

The blood from mouse, rat, dog, monkey, or human was incubated with Laz (0.5 μmol/L) at 37°C for 60 minutes, and the distribution of Laz in blood cells was determined. The blood to plasma concentration ratios of Laz in mouse, rat, dog, monkey, and human were 0.991, 0.955, 1.42, 1.75, and 1.15, respectively. The applicant explained that the above results indicated limited distribution of Laz to blood cells in human.

4.2.2.4 Placental transfer to fetus

Placental and fetal transfer of Laz has not been investigated. The applicant explained that since a rat embryo-fetal development study showed a reduction in fetal weight [see Section 5.2.5] etc., Laz may cross the placenta into the fetus.

4.2.3 Metabolism

4.2.3.1 *In vitro*

Rat, dog, or human hepatocytes were incubated with ^{14}C-Laz (10 μmol/L) at 37°C for 6 hours,[20)] and the metabolites of Laz were identified. No human specific metabolites were detected. As the primary metabolites in human hepatocytes, M11 (a glutathione conjugate), M12 (a cysteinylglycine conjugate), and M14 (a cysteine conjugate) were detected. Human hepatocytes were incubated with ^{14}C-Laz (10 μmol/L) in the presence of a CYP3A inhibitor (ketoconazole) at 37°C for 6 hours. The fractional contribution of CYP3A to the metabolism of Laz was 21%.

The following studies on metabolizing enzymes of Laz in humans were conducted.

- Recombinant human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9,

[20)] Rat and dog hepatocytes were incubated for 4 hours.

CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5) were incubated with Laz (1 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 2 hours, and CYP isoforms involved in the metabolism of Laz were identified. The fractional contributions of CYP1A2, CYP2A6, CYP2C9, CYP2E1, and CYP3A4 to the oxidative metabolism of Laz were 2.38%, 1.72%, 3.46%, 1.72%, and 88.4%, respectively, and the fractional contributions of other CYP isoforms tested were <1%.

- Recombinant human glutathione *S*-transferase (GST) isoforms (GST A1-1, GST P1-1, GST M1-1) were incubated with ^{14}C-Laz (10 μmol/L) in the presence of glutathione at 37°C for 2 hours,[21)] and the CL_{int} of Laz was determined. In the presence of GST A1-1, GST P1-1, and GST M1-1, the CL_{int} values of Laz were 0.12, 0.13, and 5.13 μL/min/μg, respectively.

The applicant's explanation:
The above results showed that CYP3A is mainly involved in the oxidative metabolism of Laz, and that GST M1-1 is mainly involved in the glutathione conjugation of Laz.

Pharmacokinetic interactions between Laz and CYP3A inhibitors or inducers are described in Section "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors or inducers."

4.2.3.2 *In vivo*

Intact or bile duct cannulated male rats received a single oral dose of ^{14}C-Laz 10 mg/kg, and its metabolites in plasma, urine, feces, and bile were identified. The results are shown below.

- In the plasma collected up to 48 hours post-dose from intact male rats, unchanged Laz was the major component detected (accounting for 49% of the total radioactivity AUC_{last} in plasma). In the urine collected up to 24 hours post-dose, M14 was mainly detected (representing 0.65% of the administered radioactivity). In the feces collected up to 48 hours post-dose, unchanged Laz, M14, and M15 (fused morpholino-benzimidazole with net loss of C_3H_6O) were mainly detected (representing 8.93%, 9.24%, and 5.62% of the administered radioactivity, respectively).
- In the bile collected up to 48 hours post-dose from bile duct cannulated male rats, M14 was mainly detected (9.44% of the administered radioactivity), and unchanged Laz was also detected (0.04% of the administered radioactivity).

4.2.4 Excretion

4.2.4.1 Urinary, fecal, and biliary excretion

Intact or bile duct cannulated male rats received a single oral dose of ^{14}C-Laz 10 mg/kg, and the recoveries of radioactivity in urine, feces, and bile (the percentage of the administered radioactivity) were determined. In intact male rats, 3.54% and 102.2% of the administered radioactivity were recovered in urine and feces, respectively, over 168 hours. In bile duct cannulated male rats, 4.38%, 23.9%, and 60.0% of the administered

[21)] GST M1-1 was incubated for 60 minutes.

radioactivity were recovered in urine, feces, and bile, respectively, over 48 hours. The applicant explained that the above results indicated that Laz is excreted predominantly in feces via bile.

4.2.4.2 Excretion into milk

Laz excretion in milk has not been investigated. The applicant explained that taking account of the physicochemical properties of Laz (molecular weight [free base], 554.7; logP value >4.0) etc., Laz may be excreted in milk.

4.2.5 Pharmacokinetic interactions

4.2.5.1 Enzyme inhibition

The applicant's explanation:

Given the following study results, the steady-state unbound C_{max} of Laz following the proposed dosing regimen of Laz (9.3 nmol/L[22)]), and the cutoff values etc. in "Drug interaction guideline for drug development and labeling recommendations" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018), Laz may cause pharmacokinetic interactions via inhibition of CYP3A or UGT1A1 in clinical use.

- Human liver microsomes were incubated with Laz (0.04-30 μmol/L) in the presence of the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A)[23)] and NADPH, and the potential of Laz to inhibit the CYP isoforms was evaluated. Laz inhibited the metabolism of the CYP2C9, CYP2C19, and CYP3A substrates, with IC_{50} values of 17.3, 26.3, and 5.18[24)] μmol/L, respectively. On the other hand, Laz did not cause evident inhibition of the metabolism of the substrates for other CYP isoforms tested.
- Human liver microsomes were incubated with Laz (0.04-30 μmol/L) in the presence of NADPH and then incubated with the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A),[23)] and Laz was evaluated as a time-dependent inhibitor of these CYP isoforms. Laz caused time-dependent inhibition of the metabolism of the CYP3A substrate. On the other hand, Laz did not cause evident time-dependent inhibition of the metabolism of the substrates for other CYP isoforms tested. Human liver microsomes were incubated with Laz (0.1-75 μmol/L) in the presence of NADPH and then incubated with a CYP3A substrate (midazolam). The K_I and k_{inact} values were 17.1 μmol/L and 0.0243 min^{-1}, respectively.
- Human liver microsomes were incubated with Laz (0.1-500 μmol/L) in the presence of the substrates for uridine diphosphate glucuronosyl transferase (UGT) isoforms (UGT1A1, UGT1A6, UGT2B7)[25)] and uridine diphosphate glucuronic acid (UDPGA), and the potential of Laz to inhibit the UGT isoforms was evaluated. Laz inhibited the metabolism of the substrates for UGT1A1 and UGT1A6, with IC_{50} values of 1.63 and 202[26)] μmol/L, respectively. On the other hand, Laz did not cause evident inhibition of the metabolism of the UGT2B7 substrate.

[22)] Calculated based on the C_{max} of Laz on Day 22 following oral administration of Laz 240 mg QD in a foreign phase I/II study (Study NSC2001) [see Section 6.2.2.2.1] and conservatively set fraction unbound in plasma in humans (0.01) [see Section 4.2.2.2].

[23)] Phenacetin, bupropion, amodiaquine, tolbutamide, *S*-mephenytoin, and dextromethorphan were used as the substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively. Midazolam and testosterone were used as CYP3A substrates.

[24)] The IC_{50} value when testosterone was used as a CYP3A substrate. When midazolam was used, the IC_{50} value was 8.07 μmol/L.

[25)] Estradiol and zidovudine were used as the substrates of UGT1A1 and UGT2B7, respectively. Acetaminophen and serotonin were used as UGT1A6 substrates.

[26)] The IC_{50} value when acetaminophen was used as a substrate of UGT1A6. Laz did not cause evident inhibition of the metabolism of serotonin.

4.2.5.2 Enzyme induction

Human hepatocytes were incubated with Laz (0.03-8 μmol/L) for 72 hours, and the mRNA expression levels of CYP isoforms (CYP1A2, CYP2B6, CYP3A4), etc., were determined. The increases in the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 caused by Laz were up to 8.8%, 46%, and 12.6%, respectively, of those caused by the respective positive controls.[27)] The increases in the activities of CYP1A2, CYP2B6, and CYP3A4 caused by Laz were up to 40%, 21%, and 3.6%, respectively, of those caused by the respective positive controls.

The applicant's explanation:
Given the above results, the steady-state unbound C_{max} of Laz following the proposed dosing regimen of Laz (9.3 nmol/L[22)]), and "Guideline on drug interaction studies" (PSB/PED Notification No. 1127-2 dated November 27, 2024), Laz may cause pharmacokinetic interactions via induction of CYP1A2 or CYP3A4 in clinical use.

Pharmacokinetic interactions between Laz and CYP3A substrates are described in Sections "6.2.2.3 Drug interaction studies" and "6.R.3 Pharmacokinetic interactions with CYP3A, BCRP, or OCT1 substrates."

4.2.5.3 Transporters

The results of the following studies showed that Laz is a substrate of p-glycoprotein (P-gp).

- Using the canine kidney MDCKII cell line expressing human P-gp, P-gp-mediated transport of Laz (1 μmol/L) was investigated. The efflux ratios of Laz were 1.36 and 3.23 in the presence and absence of a P-gp inhibitor (valspodar 10 μmol/L), respectively.
- Using the MDCKII cell line expressing human breast cancer resistance protein (BCRP), BCRP-mediated transport of Laz (0.1-10 μmol/L) was investigated. The ratio of the efflux ratio of Laz in the BCRP-expressing cell line to the efflux ratio in the parental cell line was 0.70 to 1.61.
- Using the membrane vesicles from the human embryonic kidney HEK293 cell line expressing human bile salt export pump (BSEP), multidrug resistance associated protein 2 (MRP2), or MRP4, each transporter-mediated transport of Laz (0.1-100 μmol/L[28)]) was investigated. In all membrane vesicles, the ratio of the uptake of Laz in the presence of ATP relative to the absence of ATP was <2.
- Using the HEK293 cell line expressing human apical sodium-dependent bile acid transporter (ASBT), organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 (OCT1), or OCT2, or the MDCKII cell line expressing human multidrug and toxin extrusion 1 (MATE1) or MATE2-K, each transporter-mediated transport of Laz (0.05-50 μmol/L) was investigated. The ratio of the uptake rate of Laz in each transporter-expressing cell line to the uptake rate of Laz in the parental cell line was <2.

[27)] Omeprazole (0.5-100 μmol/L), phenobarbital (5-1,000 μmol/L), and rifampicin (0.1-20 μmol/L) were used as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.
[28)] The concentrations tested for MRP4 were 1 to 10 μmol/L.

The applicant's explanation:

Given the following study results, the steady-state unbound C_{max} of Laz following the proposed dosing regimen of Laz (9.3 nmol/L[22)]), and the cutoff values etc. in "Drug interaction guideline for drug development and labeling recommendations" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018), Laz may cause pharmacokinetic interactions via inhibition of OCT1 or BCRP in clinical use.

- Using the MDCKII cell line expressing human P-gp, the potential of Laz (10 μmol/L) to inhibit P-gp-mediated transport of digoxin (5 μmol/L) was evaluated. The efflux ratios of the P-gp substrate in the presence and absence of Laz were 11.0 and 22.5, respectively.
- Using the membrane vesicles from the HEK293 cell line expressing human BCRP, BSEP, MRP2, or MRP4, the potential of Laz (0.05-100 μmol/L[29)]) to inhibit the transport of the substrate of each transporter[30)] was evaluated. Laz inhibited the transport of the substrates of BCRP, BSEP, and MRP4, with IC_{50} values of 0.25, 5.00, and 12.5 μmol/L, respectively. On the other hand, Laz did not cause evident inhibition of the transport of the substrate of MRP2.
- Using the HEK293 cell line expressing human ASBT, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2, or the MDCKII cell line expressing human MATE1 or MATE2-K, the potential of Laz (0.041-30 μmol/L) to inhibit the transport of the substrate of each transporter[31)] was evaluated. Laz inhibited the transport of the substrates of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K, with IC_{50} values of 8.26, 17.7, 0.31, 13.41, 5.79, and 3.16 μmol/L, respectively. On the other hand, Laz did not cause evident inhibition of the transport of the substrates of other transporters.

Pharmacokinetic interactions via inhibition of OCT1 or BCRP are described in Sections "6.2.2.3 Drug interaction studies" and "6.R.3 Pharmacokinetic interactions with CYP3A, BCRP, or OCT1 substrates."

4.2.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of Laz is acceptable.

4.2.R.1 Pharmacokinetic interactions of Laz

The applicant's explanation about pharmacokinetic interactions of Laz:

The results of *in vitro* studies indicated that Laz causes pharmacokinetic interactions via inhibition of UGT1A1 or induction of CYP1A2 in clinical use [see Sections 4.2.5.1 and 4.2.5.2]. However, the physiologically based pharmacokinetics (PBPK) modeling predicted the lack of a marked effect of Laz on raltegravir (a substrate of UGT1A1) or caffeine (a substrate of CYP1A2) exposure. Given this finding, among others, coadministration with a substrate of UGT1A1 or a substrate of CYP1A2 is unlikely to become a problem in the clinical use of Laz.

[29)] The concentrations tested for BCRP and MRP4 were 0.05 to 40 μmol/L, and the concentrations tested for BSEP and MRP2 were 0.14 to 100 μmol/L.

[30)] Estrone-3-sulfate (1 μmol/L), taurocholic acid (0.2 μmol/L), estradiol-17β-glucuronide (100 μmol/L), and dehydroepiandrosterone sulfate (0.5 μmol/L) were used as the substrates of BCRP, BSEP, MRP2, and MRP4, respectively.

[31)] (1) Taurocholic acid (5 μmol/L), (2) estradiol-17β-glucuronide (1 μmol/L), (3) cholecystokinin-8 (1 μmol/L), (4) tenofovir (5 μmol/L), (5) methotrexate (1 μmol/L), and (6) metformin (10 μmol/L) were used as the substrates of (1) ASBT, (2) OATP1B1, (3) OATP1B3, (4) OAT1, (5) OAT3, and (6) OCT1, OCT2, MATE1, and MATE2-K.

Although the results of an *in vitro* study showed that Laz is a substrate of P-gp [see Section 4.2.5.3], since a global phase III study (MARIPOSA study) raised no particular safety concerns about coadministration with a P-gp inhibitor, etc., coadministration with a P-gp inhibitor is unlikely to become a problem in the clinical use of Laz.

PMDA's view:
PMDA largely accepted the applicant's explanation. However, since the results of *in vitro* studies concerning Laz pharmacokinetic interactions via inhibition of UGT1A1, induction of CYP1A2, or P-gp are important for the propose use of Laz, information on the results of these studies should be provided appropriately to healthcare professionals in clinical practice using the package insert. Relevant information should be collected, and if useful information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

5. Toxicology and Outline of the Review Conducted by PMDA

5.1 Ami

Since the present application is intended for a new indication and a new dosage, no toxicology data have been submitted.

5.2 Laz

In this section, unless otherwise specified, the doses and concentrations of Laz are expressed as free base.

5.2.1 Single-dose toxicity

Single oral or intravenous dose toxicity studies in rats were conducted (Table 14). Following intravenous administration, no acute symptoms were observed. Following oral administration, early sacrifice due to deterioration in clinical signs occurred. The approximate lethal doses of Laz by oral and intravenous administration were determined to be 2,000 mg/kg and >20 mg/kg, respectively.

Table 14. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg/day)	Noteworthy findings	Approximate lethal dose (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral gavage	0,*1 200, 600, 2,000	≥200: decreases in body weight/food consumption 2,000: early sacrifice due to deterioration in clinical signs*3	2,000	4.2.3.1.1
Male and female rats (Sprague Dawley)	IV	0,*2 20	No acute symptoms	>20	4.2.3.1.2

*1 0.5% methylcellulose and 50 mmol/L citric acid in reverse osmosis water (pH 3.0-3.2), *2 50 mmol/L citric acid in saline (pH 2.0)
*3 Early group sacrifice on Day 8 due to deterioration in clinical signs at 2,000 mg/kg

5.2.2 Repeated-dose toxicity

Four-week and 13-week repeated-dose toxicity studies in rats and dogs were conducted (Table 15). The noteworthy toxicity findings observed in both rats and dogs were mortality associated with systemic toxicity, corneal atrophy, skin lesions such as acanthosis and ulcer, blunting/fusion of villi in the duodenum,

tubular degeneration in the testis, luminal cellular debris in the epididymis, and hypercellular femoral and sternal bone marrow. In rats, alveolar macrophage infiltration in the lung, hepatocyte necrosis in the liver, renal tubular dilation/papillary necrosis of the kidney, atrophy of the uterus and vagina, and femoral epiphyseal hypertrophy were observed. In dogs, fibrosis/hemorrhage/thrombus in the heart, degeneration/necrosis of the myocardium and vessel in the heart, inflammation/hyperplasia of alveolar type II cells in the lung, esophageal epithelial atrophy, blunting/fusion of villi in the jejunum, mononuclear cell infiltration in the liver, inflammation/infarct in the kidney, epithelial atrophy/decreased secretion in the prostate, and mixed cell inflammation in the epididymis were observed. The findings observed at the low dose levels in the 4-week and 13-week repeated-dose toxicity studies in rats were all considered of little toxicological significance, because of the severity of the findings or the absence of associated findings.

The applicant's explanation about the observed findings that were not considered related to or secondary to EGFR inhibition by Laz:

- As to hypercellular femoral and sternal bone marrow and epiphyseal hypertrophy observed in rats, EGFR expression in the cartilage, bone, bone marrow, or hematopoietic cells has not been reported, and no relevant serious adverse events occurred also in clinical studies of Laz. Thus, a safety problem is unlikely to occur in the clinical use of Laz.
- As to renal tubule cell carcinoma observed in dogs, spontaneous renal cell carcinoma in juvenile dogs aged <2 years has been reported (*Can Vet J*. 2004; 45: 860-2, *J Am Anim Hosp Assoc*. 1995; 31: 29-33, *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. Elsevier; 2007. p498-50), and there is no report on assessment of the relationship between EGFR inhibition and renal tubular carcinoma or renal cell carcinoma. Thus, this finding is considered incidental.

The no-observed-adverse-effect level (NOAEL) in the 13-week repeated-dose toxicity study in rats was determined to be 25 mg/kg/day. Since toxicity findings were observed at the lowest dose level in the 13-week repeated-dose toxicity study in dogs, a NOAEL was not established. Laz plasma exposure (AUC_{24h}) after repeated dosing at the NOAEL in rats was 11,600 ng·h/mL in males and 17,500 ng·h/mL in females, which were approximately 1.8-fold and approximately 2.7-fold the human exposure,[32)] respectively.

[32)] The AUC_{24h} on Day 22 following oral administration of Laz 240 mg QD in a foreign phase I/II study (Study NSC2001) (6,542 ng·h/mL) [see Section 6.2.2.2.1]

Table 15. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral gavage	4 weeks + 2-week recovery period	0,[*1] 25, 50, 100/75[*2]	<u>Unscheduled sacrifice</u> 100/75: 1/15 (female) thin appearance, hunched posture, squinting of eyes, piloerection, dehydration, black feces, stains around the nares, scabs on the hind legs, renal tubular dilation/papillary necrosis of the kidney, erosion/ulcer/mixed cell inflammation/hair follicle degeneration/exudate in the skin/subcutis, decreased corpora lutea of the ovary, atrophy of the uterus, vaginal atrophy/exudate <u>Scheduled sacrifices</u> ≥25: increased AST, decreased A/G ratio (male and female), increased blood inorganic phosphorus, large mandibular lymph nodes, epidermal surface exudate (male), decreases in hemoglobin/hematocrit, increased reticulocyte count, increased ALT, decreases in blood albumin/calcium, decreased heart weights (female) ≥50: decreased food consumption, increases in neutrophil count/platelet count, increases in blood urea nitrogen/potassium, scabs/hair follicle degeneration/acanthosis/erosion/ulcer/infiltration of mixed inflammatory cells in the skin, corneal atrophy, blunting/fusion of villi in the duodenum, lymphocyte hyperplasia of the mandibular lymph node (male and female), decreases in body weight/body weight gain, decreases in blood albumin/calcium, Kupffer cell hypertrophy in the liver, luminal cellular debris in the epididymis (male), clear oral discharge, decreased red blood cell count, increased monocyte count, increases in blood inorganic phosphorus/globulin, decreased uterine weights, large mandibular lymph nodes, epidermal surface exudate, femoral epiphyseal hypertrophy, decreased corpora lutea , atrophy of the uterus/vagina (female) 100/75: thinning haircoat, increased kidney weights, extramedullary hematopoiesis in the liver, renal tubular dilation, hypercellular femoral/sternal bone marrow (male and female), clear oral discharge, decreases in red blood cell count/hemoglobin/hematocrit, increases in reticulocyte count/monocyte count/white blood cell count, increased blood globulin, decreased blood triglycerides, decreased urine pH, decreases in epididymis/prostate weights, hepatocyte necrosis, femoral epiphyseal hypertrophy, tubular degeneration in the testis (male), decreases in body weight/body weight gain, decreases in MCV/MCHC, increased large unstained cell count, increased blood creatinine, increased salivary gland weights, papillary necrosis of the kidney (female)	25	4.2.3.2.3
				After recovery period[*5] 100/75: decreases in blood albumin/A/G ratio, increased blood globulin, large mandibular lymph nodes, fibrosis in the skin, lymphocyte hyperplasia of the mandibular lymph node (male and female), centrilobular hepatocyte vacuolation/Kupffer cell hypertrophy/hepatocyte necrosis in the liver, hair follicle degeneration/mixed cell inflammation in the skin, tubular degeneration in the testis, luminal cellular debris/decreased luminal sperm in the epididymis (male), increased spleen weights (female)		

Male and female rats (Sprague Dawley)	Oral gavage	13 weeks + 8-week recovery period	0[*3], 12.5,[*4] 25,[*4] 50[*4]	<u>Mortalities or unscheduled sacrifices</u> 50: 3 of 15 animals (female) thin appearance, swollen periorbital region, excessive salivation, brown discolored skin on the nose, thinning/rough haircoat, increases in white blood cell count/neutrophil count/monocyte count/large unstained cell count, increases in blood total protein/globulin, decreases in blood albumin/A/G ratio, increases in blood ALT/AST, increases in blood urea nitrogen/inorganic phosphorus/potassium, alveolar macrophage infiltration, Kupffer cell hyperplasia in the liver, fusion of villi in the duodenum, degeneration/necrosis in the perianal sebaceous glands, lymphocyte hyperplasia of the mandibular lymph node, granulomatous inflammation/hair follicle degeneration in the skin/subcutis, papillary necrosis of the kidney, atrophy of the uterus/vagina, hypercellular sternal/femoral bone marrow, corneal atrophy/erosion/ulcer, erosion/ulcer/epidermal surface exudate/chronic active inflammation in the eyelids, necrosis of lymphocytes in the thymus <u>Scheduled sacrifices</u> ≥12.5: increases in blood AST/potassium, degeneration/necrosis in the perianal sebaceous glands (male and female), increased blood ALT, positive urine occult blood (male), increased heart weights (female) ≥25: increased neutrophil count, decreased A/G ratio, granulomatous inflammation in the hair follicle, alveolar macrophage infiltration (male and female), increased platelet count, increased spleen weights (male), decreases in body weight gain/food consumption, increases in white blood cell count/monocyte count/basophil count, increased blood urea nitrogen, increased kidney weights, hair follicle degeneration, atrophy of the vagina (female) 50: clear oral discharge, decreased hemoglobin, increased large unstained cell count, increases in blood fibrinogen/globulin/inorganic phosphorus, decreased blood albumin, large mandibular lymph nodes/lymphocyte hyperplasia of the mandibular lymph node, corneal atrophy, Kupffer cell hyperplasia in the liver, blunting/fusion of villi in the duodenum (male and female), decreased body weight gain, decreases in hematocrit/MCH, increases in reticulocyte count/white blood cell count/lymphocyte count /monocyte count/basophil count, increased blood urea nitrogen, increased kidney weights, hair follicle degeneration (male), decreased blood calcium, increases in liver/brain/stomach weights, decreases in uterus/cervix weights, papillary necrosis of the kidney, decreased corpora lutea of the ovary, atrophy of the uterus (female)	25	4.2.3.2.5
				After recovery period[*5] 50: decreased corpora lutea of the ovary (female)		
Male and female dogs (Beagle)	Oral gavage	4 weeks + 2-week recovery period	0,[*1] 5, 10, 20	<u>Unscheduled sacrifice</u> 20: 1 of 5 animals (male) hypoactivity, shivering, dehydration, hyperthermia, prone position, decreased food consumption, premature ventricular complexes, fibrosis/hemorrhage/thrombus in the heart, degeneration/necrosis of the myocardium, vascular/perivascular inflammation in the brain/epididymis/kidney/spinal cord/urinary bladder, degeneration/necrosis in the femur/sternal bone marrow/epididymis, necrosis of the vessel walls within the meninges, mixed cell inflammation in the aorta <u>Scheduled sacrifices</u> ≥5: esophageal epithelial atrophy, epithelial atrophy in the cornea (male and female), increased blood globulin, decreased A/G ratio, tubular degeneration in the testis, hypercellular femoral/sternal bone marrow, mononuclear cell infiltration in the liver (male), vocalization during dosing,[*6] decreased blood albumin (female) ≥10: liquid feces, decreased lymphocytes in the mandibular lymph node (male and female), decreased thymus weights, mixed cell inflammation/luminal cellular debris/reduced luminal sperm in the epididymis, decreased secretion in the prostate, decreased lymphocytes in the thymus (male), excessive salivation,[*6] decreased blood total protein, decreased lymphocytes in GALT, hypercellular sternal bone marrow, mononuclear cell infiltration in the liver (female) 20: blunting/fusion of villi/epithelial hyperplasia in the duodenum, atrophy in the skin, decreased lymphocytes in the mesenteric lymph node (male and female), excessive salivation, vocalization during dosing, decreased food consumption, increases in blood fibrinogen/troponin I, decreases in testis/epididymis/prostate weights, fibrosis/hemorrhage/thrombus/mixed cell inflammation in the heart, degeneration/necrosis of the myocardium and vessel in the heart, neutrophil infiltrates/erosion/ulcer/hemorrhage in the duodenum, decreased lymphocytes in GALT (male), inflammation in the pelvis (female)	—[*8]	4.2.3.2.8
				These findings were reversible.		

Male and female dogs (Beagle)	Oral gavage	13 weeks + 8-week recovery period	0,[*3] 2,[*4] 4,[*4] 8[*4]	Unscheduled sacrifice 8: 1 of 5 animals (male) thin appearance, hunched posture, lateral recumbency, muscular atrophy, decreased body weight, decreased red blood cell count, increases in blood cholesterol/triglycerides/ALP, decreases in creatine kinase/blood inorganic phosphorus, chronic active inflammation/hyperplasia of alveolar type II cells in the lung, increased lymphocytes/acute inflammation in the mediastinal lymph node, leukocytosis in the liver, decreased lymphocytes in the mesenteric lymph node/thymus, decreased zymogen granules in the pancreas, prostate epithelial atrophy/esophageal epithelial atrophy Scheduled sacrifices 2: active inflammation in the kidney (male) ≥4: decreased A/G ratio, esophageal epithelial atrophy, vascular/perivascular inflammation in the epididymis[*7] (male), chronic active inflammation/ hyperplasia of alveolar type II cells in the lung[*7] (female) 8: decreased zymogen granules in the pancreas (male and female), decreases in red blood cell count/hemoglobin/hematocrit, decreases in blood albumin/calcium, chronic active inflammation/hyperplasia of alveolar type II cells in the lung, prostate epithelial atrophy, decreased lymphocytes in the thymus cortex/mesenteric lymph node, increased lymphocytes/acute inflammation in the mediastinal lymph node, leukocytosis in the liver, vascular/perivascular inflammation in the urinary bladder (male), increased blood globulin, renal tubule cell carcinoma, blunting/fusion of villi in the jejunum (female)	(Males) —[*8] (Females) 2	4.2.3.2.9
				After recovery period: 8: chronic active inflammation/hyperplasia of alveolar type II cells in the lung, infarct/chronic active inflammation in the kidney (female)		

*1 0.5% methylcellulose and 50 mmol/L citric acid in reverse osmosis water (pH 3.0-3.2)
*2 The dose was reduced from 100 mg/kg to 75 mg/kg on Day 21. *3 0.5% methylcellulose in reverse osmosis water
*4 Doses as the mesilate salt of lazertinib, *5 The persistent findings only are listed.
*6 Excluding 20 mg/kg, *7 Excluding 8 mg/kg, *8 A NOAEL was not established.

5.2.3 Genotoxicity

A bacterial reverse mutation assay (Ames assay), a chromosomal aberration assay in Chinese hamster lung cells, and a rat micronucleus assay were conducted, and Laz showed no genotoxic potential (Table 16).

Table 16. Genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentrations or doses	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9−	0,[*1] 2.5, 8, 23, 70, 200 μg/plate	Negative	4.2.3.3.1.1
			S9+	0,[*1] 2.5, 8, 23, 70, 200 μg/plate	Negative	
	Chromosomal aberration assay	Chinese hamster lung cells (CHL cells)	S9− (6 hours)	0,[*1] 0.5, 1, 2, 3, 4 μg/mL	Negative	4.2.3.3.1.2
			S9+ (6 hours)	0,[*1] 5, 10, 12.5, 15, 16 μg/mL	Negative	
			S9− (22 hours)	0,[*1] 0.25, 0.5, 1, 2, 2.5 μg/mL	Negative	
In vivo	Micronucleus assay	Male rat (Sprague Dawley), 2 days (once daily), oral gavage, bone marrow		0,[*2] 500, 1,000, 2,000 mg/kg	Negative	4.2.3.3.2.1

*1 DMSO, *2 0.5% methylcellulose and 50 mmol/L citric acid in reverse osmosis water (pH 3.0-3.2)

5.2.4 Carcinogenicity

No carcinogenicity studies were conducted because Laz is an anti-neoplastic drug intended to treat patients with advanced cancer.

5.2.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats and embryo-fetal development studies in rats and rabbits were conducted (Table 17).

In the study of fertility and early embryonic development to implantation in rats, there were no effects on male or female fertility, and a lower number of viable fetuses and an increase in post-implantation loss were observed in the Laz 30 mg/kg group. In the embryo-fetal development studies in rats and rabbits, decreased fetal weights or skeletal abnormalities were observed. The findings observed in parental animals in the study of fertility and early embryonic development to implantation and in dams at the low or intermediate doses in the embryo-fetal development studies were all considered of little toxicological significance, because of the severity of the findings or the absence of associated findings. The NOAELs for embryo-fetal development were determined to be 30 mg/kg in rats and 45 mg/kg in rabbits. Laz plasma exposure (AUC_{24h}) at the NOAEL was 11,100 ng·h/mL in rats and 3,240 ng·h/mL in rabbits, which were approximately 1.7-fold and approximately 0.5-fold the human exposure, [32)] respectively.

The applicant's explanation:
Based on the above study results, the package insert and other materials will appropriately advise healthcare professionals in clinical practice about the following: (1) Females with reproductive potential should be advised to use effective contraception during treatment with Laz and for 3 weeks[33)] after the last dose of Laz; and (2) Laz may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.

[33)] On the basis of "Guidance on the need for contraception related to the use of pharmaceuticals" (PSEHB/PED Notification No. 0216-1 and PSEHB/PSD Notification No. 0216-1, dated February 16, 2023), a contraception period of >5 × $t_{1/2}$ (64.7 hours, see Section 6.2.2.2.1) on Day 1 following administration of Laz 240 mg QD in a foreign phase I/II study (Study NSC2001) (323.5 hours) was recommended.

Table 17. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Dose[*1] (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (Sprague Dawly)	Oral gavage	Males dosed for 29 days prior to mating, throughout mating, and through the day prior to sacrifice Females dosed for 15 days prior to mating, throughout mating, and through gestation day 7	0,[*2] 7.5, 15, 30	Parental animals: 30: decreases in body weight gain/food consumption (male and female), rough haircoat, scabbing, thinning haircoat, decreased epididymis weights[*3] (male), scabbing (female) Fertility/early embryonic development: 30: decreased sperm motility[*4] (male), a lower number of viable fetuses, an increase in post-implantation loss (female)	Parental general toxicity: 30 Fertility, early embryonic development:15	4.2.3.5.1.1.
Embryo-fetal development	Female rat (Sprague Dawley)	Oral gavage	From gestation day 6 through 17 (QD) C-section performed on gestation day 21	0,[*2] 7.5, 30, 60	Dams: ≥7.5: rough haircoat ≥30: scabbing, decreases in body weight gain/food consumption 60: decreased body weight Embryos/fetuses: 60: decreased fetal weights	Maternal general toxicity: 30 Embryos/fetuses: 30	4.2.3.5.2.2
	Female rabbit (NZW)	Oral gavage	From gestation day 7 through 19 (QD) C-section performed on gestation day 29	0,[*2] 5, 25, 45	Dams: <u>Mortalities and unscheduled sacrifices</u> 45: 5 of 23 animals no food consumption, decreases in body weight/food consumption <u>Surviving animals</u> ≥25: decreased feces, decreases in body weight gain/food consumption 45: decreased body weight Embryos/fetuses: 45: misaligned caudal vertebra[*5, *7] unossified hyoid bone[*6, *7]	Maternal general toxicity: 25 Embryos/fetuses: 45	4.2.3.5.2.4

*1 Doses as the mesilate salt of lazertinib, *2 0.5% methylcellulose in reverse osmosis water
*3 The finding was associated with decreased body weight and was considered of little toxicological significance.
*4 The finding was observed in 1 of 22 animals, but was considered of little toxicological significance because this 1 male was fertile, and there were no effects on sperm concentration or male fertility at 30 mg/kg.
*5 Malformations, *6 Variations
*7 The findings were considered of little toxicological significance because comparison with the control group showed no statistically significant differences.

5.2.6 Other toxicity studies

5.2.6.1 Photosafety

As Laz absorbs light at the wavelengths of 290 to 700 nm, phototoxicity studies using mouse fibroblasts or pigmented rats were conducted (Table 18). The applicant explained that since no findings indicative of phototoxicity were observed, Laz has little phototoxic potential.

Table 18. Photosafety studies

Type of study	Test system	Test method	Result	Attached document CTD
In vitro	Mouse fibroblasts (BALB/c 3T3)	0,[*1] 7.81, 15.63, 31.25, 62.5, 125, 250, 500, and 1,000 µg/mL UVA (5 J/cm^2) radiation	PIF = 1, MPE = −0.031, −0.006 Not phototoxic	4.2.3.7.7.1
In vivo	Pigmented rat (Long-Evans)	Oral gavage doses of 0,[*2] 25, 50, or 75 mg/kg for 6 days UVA (10 J/cm^2) and UVB (145 J/cm^2) radiation[*3]	NOAEL for phototoxicity: 50 mg/kg	4.2.3.7.7.2

*1 Ethanol, *2 0.5% methylcellulose in reverse osmosis deionized water
*3 All animals in the 75 mg/kg group were not exposed to UVR due to serious skin reactions.

5.2.6.2 Skin sensitization and ocular irritation studies

As an *in vivo* skin sensitization study, a local lymph node assay in mice was conducted, and Laz was classified as a skin sensitizer (Table 19). As an *in vitro* ocular irritation study, the bovine corneal opacity and permeability test was conducted, and Laz fell in the category of "no prediction can be made" (Table 19).

Table 19. Overview of skin sensitization and ocular irritation studies

Type of study		Test system	Test method	Noteworthy findings	Attached document CTD
In vitro	Bovine corneal opacity and permeability test (BCOP)	Isolated bovine cornea	Laz 320.9 to 345.6 mg was applied topically to the epithelium of isolated bovine corneas for 4 hours, and then corneal permeability and opacity were measured.	Irritancy score = 7.8 GHS category: No stand-alone prediction can be made	4.2.3.7.7.4
In vivo	Local lymph node assay (LLNA)	Female mouse (CBA/J)	0%,[*] 2%, 10%, or 30% Laz in DMSO was applied onto the dorsal regions of both ears QD for 3 days.	SI ≥3 Laz was classified as a skin sensitizer.	4.2.3.7.7.3

*Vehicle control

5.2.6.3 Qualification assessment of impurities

When the drug substance manufactured by the process [redacted] [see Section 2.2.1.2] was tested for release and under long-term storage conditions, Impurity A was present at a level greater than the reporting threshold (0.05%) specified in the ICH Q3A guideline. Impurity B may arise from [redacted] during the manufacturing process. Four-week repeated-dose toxicity studies in rats were conducted to qualify Impurity A and Impurity B, and no toxicity findings considered related to the impurities were observed (Table 20).

Table 20. Overview of impurity studies

Test system	Route of administration	Duration of dosing	Dose[*1] (mg/kg/day)	Noteworthy findings	Attached document CTD
Male rat (Sprague Dawley)	Oral gavage	4 weeks (QD)	0,[*2] 25, 25[*3]	No toxicity findings related to the impurity were observed.	4.2.3.7.6.1
Male and female rats (Sprague Dawley)	Oral gavage	4 weeks (QD)	0,[*2] 25, 25[*4]	No toxicity findings related to the impurity were observed.	4.2.3.7.6.2

*1 Doses as the mesilate salt of lazertinib
*2 0.5% (w/v) methylcellulose in reverse osmosis water (pH 3)
*3 Containing [redacted]% Impurity A
*4 Containing [redacted]% Impurity B

5.2.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the toxicity of Laz is acceptable.

5.2.R.1 Systemic toxicities

The applicant's explanation about the effects of Laz in rats or dogs occurring at dose levels corresponding to exposure levels close to the human exposure [lung effects (alveolar macrophage infiltration, inflammation, hyperplasia of alveolar type II cells), cardiovascular effects (fibrosis/hemorrhage/thrombus in the heart, degeneration/necrosis of the myocardium and vessel), skin lesions (inflammation, ulcer, etc.), hepatocyte necrosis, gastrointestinal lesions (esophageal epithelial atrophy, blunting/fusion of villi in the duodenum and jejunum, ulcer in the jejunum, etc.), corneal atrophy, effects on male and female reproductive organs (tubular degeneration in the testis, mixed cell inflammation/luminal cellular debris/decreased luminal sperm in the epididymis, decreased secretion in the prostate, atrophy of the uterus and vagina), and renal effects (renal tubular dilation, papillary necrosis and infarct of the kidney)]:

- EGFR has been reported to be expressed in epithelial cells in systemic tissues and organs, etc. and involved in the normal development and proliferation of epithelial cells, etc. (*Oncol Nurs Forum.* 2016; 43: 235-43, *EMBO J.* 1998; 7: 719-31, etc.). The above findings may have been associated with the inhibition of turnover and proliferation of epithelial cells resulting from the inhibition of EGFR by Laz.
- With respect to effects on the lung, cardiovascular system, skin tissue, liver, gastrointestinal tract, and cornea observed in rats or dogs, interstitial lung disease (ILD) [see Section 7.R.3.3], arterial thromboembolism [see Section 7.R.3.5], hepatic dysfunction [see Section 7.R.3.6], gastrointestinal disorders [see Section 7.R.3.7], skin disorders [see Section 7.R.3.8], cardiac failure [see Section 7.R.3.9], and eye disorders [see Section 7.R.3.10] were reported as relevant adverse events in clinical studies. Given that among the above adverse events, ILD and skin disorders are known risks associated with the existing epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), a relevant precautionary statement will be included in the Laz package insert. As to hepatic dysfunction and eye disorders, taking account of the incidences of these events in clinical studies, information on the incidences of increased ALT/increased AST and keratitis in clinical studies will be included in the Laz package insert. On the other hand, as to cardiovascular effects, taking account of the incidence of adverse events related to cardiovascular disorders in clinical studies [see Section 7.R.3.1], a relevant precautionary statement in the Laz package insert is unnecessary.
- Given that renal effects observed in rats and dogs were reversible after a recovery period, and taking account of the incidence of adverse events related to renal dysfunction in clinical studies [see Section 7.R.3.1], a safety problem is unlikely to arise in the clinical use of Laz.
- Given that effects on male and female reproductive organs observed in rats and dogs were reversible after a recovery period, and that there were no effects on male or female fertility in a rat study of fertility and early embryonic development to implantation [see Section 5.2.5], a safety problem is unlikely to arise in the clinical use of Laz.

PMDA's view:

PMDA accepted the applicant's explanation about the possibility that toxicity findings observed in rats and dogs were caused by EGFR inhibition, and the effects of Laz on the kidney and male and female reproductive organs in humans. On the other hand, the effects of Laz on the lung, cardiovascular system, skin tissue,

liver, gastrointestinal tract, and cornea were observed at exposure levels less than or close to the human exposure in repeated-dose toxicity studies. Thus, these effects in humans will be discussed in Sections "7.R.3.3 ILD," "7.R.3.5 Arterial thromboembolism," "7.R.3.6 Hepatic dysfunction," "7.R.3.7 Gastrointestinal disorders," "7.R.3.8 Skin disorders (including paronychia)," "7.R.3.9 Cardiac failure," and "7.R.3.10 Eye disorders," taking account of the incidence of adverse events in clinical studies.

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

6.1 Ami

Although the present application is intended for a new indication and a new dosage, the data on biopharmaceutic studies and associated analytical methods were previously evaluated for the initial approval of Ami, and no new study data have been submitted. Clinical pharmacology studies of Ami in combination with Laz are described in Section 6.2.2.1.

6.1.1 Clinical pharmacology

6.1.1.1 Exposure-efficacy/safety relationship

Based on the results from the Ami/Laz group in a global phase III study (MARIPOSA study), the relationships between Ami exposure and efficacy/safety were explored. Ami exposure was predicted from the PPK analysis.[34)]

6.1.1.1.1 Exposure-efficacy relationship

The relationship between Ami exposure (the pre-dose concentrations on Cycle 1 Day 8 and Cycle 2 Day 1 and C_{avg} in Cycle 1) and progression-free survival (PFS) was explored. There was no clear relationship between Ami exposure and PFS.

6.1.1.1.2 Exposure-safety relationship

The relationship between Ami exposure (the maximum C_{eoi} and C_{avg} in Cycle 1) and ILD, paronychia, hypoalbuminaemia, diarrhoea, stomatitis, paraesthesia, rash of any grade, Grade ≥3 rash, venous thromboembolism of any grade, or Grade ≥3 venous thromboembolism was explored. In addition, the relationship between Ami exposure (C_{eoi} on Day 1) and infusion reaction of any grade or Grade ≥3 infusion reaction was explored. The incidences of paronychia and stomatitis tended to increase with increasing Ami exposure. On the other hand, there was no clear relationship between Ami exposure and the incidence of ILD, hypoalbuminaemia, diarrhoea, paraesthesia, rash of any grade, Grade ≥3 rash, venous thromboembolism, or infusion reaction.

[34)] Predicted from the PPK analysis, which was performed using the nonlinear mixed-effects modeling, based on Ami PK data (1,327 subjects, 27,053 sampling points) (software used, NONMEM Version 7.4.3). The PPK model used in this analysis was developed by updating the PPK model developed based on Ami PK data obtained from a global phase I study (Study EDI1001, Ami monotherapy cohorts and Ami/CP cohort) and a global phase III study (PAPILLON study), using the pooled data from Study EDI1001 (Ami monotherapy cohorts and Ami/Laz cohort), a global phase I/Ib study (Study NSC1001), and the MARIPOSA study.

6.2 Laz

6.2.1 Summary of biopharmaceutic studies and associated analytical methods

As the oral formulation of Laz, tablets are available. The PK etc. of Laz were evaluated using the tablets (Table 21). The proposed commercial formulations are the G004 formulation (the 80-mg tablet) and the G005 formulation (the 240-mg tablet). Dissolution test performed in accordance with "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000) demonstrated the bioequivalence between these formulations.

Table 21. Formulations used in clinical studies

Formulation	Study ID
G001 formulation (80-mg tablet)	a global phase I study (Study EDI1001), a global phase I/Ib study (Study NSC1001), foreign phase I studies (Study 101, Study NSC1009), a foreign phase I/II study (Study NSC2001)
G002 formulation (80-mg tablet)	a global phase I study (Study EDI1001), a global phase I/Ib study (Study NSC1001), a global phase III study (MARIPOSA study), foreign phase I studies (Study NSC1002, Study NSC1003, Study NSC1006, Study NSC1007, Study NSC1008, Study NSC1009), a foreign phase III study (Study 301)
G004 formulation (80-mg tablet) G005 formulation (240-mg tablet)	foreign phase I studies (Study NSC1006, Study NSC1009)

Laz concentrations in human plasma were determined using an LC-MS/MS method (LLOQ, 1.00 ng/mL).

6.2.1.1 Foreign clinical studies

6.2.1.1.1 Foreign phase I study (CTD 5.3.1.2.3, Study NSC1009 [January to April 2023])

A 4-period, crossover study was conducted in 64 healthy adult subjects[35] (64 included in the PK analysis) to evaluate the bioequivalence between the G002 and G001/G004/G005 formulations. A single oral dose of Laz 240 mg was to be administered under fasting conditions,[36] and a washout period of 14 to 21 days was included between the periods.

The Laz C_{max} and AUC_{last} geometric mean ratios for (1) the G001 formulation, (2) the G004 formulation, and (3) the G005 formulation vs. the G002 formulation [90% confidence interval (CI)] were (1) 1.01 [0.950, 1.07] and 1.01 [0.962, 1.06], respectively, (2) 1.03 [0.965, 1.10] and 1.02 [0.970, 1.07], respectively, and (3) 1.10 [1.02, 1.18] and 1.07 [1.01, 1.13], respectively, all of which met the bioequivalence criteria (0.80-1.25).

The applicant explained that the above results demonstrated the bioequivalence between the G002 and G001/G004/G005 formulations.

6.2.1.1.2 Foreign phase I study (CTD 5.3.1.1.1, Study 101 [July to August 2018])

A 2-treatment, 2-period, crossover study was conducted in 24 healthy adult subjects (24 included in the PK analysis) to evaluate the effect of food on the PK of Laz. A single oral dose of Laz 240 mg was to be administered under fasting conditions [36] or at 30 minutes after a high-fat meal,[37] and a washout period of 21 days was included between the periods.

[35] 16 subjects each in the A, B, C, and D groups
[36] Subjects were to be fasted for ≥10 hours (overnight) pre-dose and for 4 hours post-dose.
[37] 800-1,000 kcal, 50% fat

The Laz C_{max} and AUC_{last} geometric mean ratios for a high-fat meal vs. fasting [90% CI] were 0.934 [0.827, 1.05] and 1.14 [1.07, 1.22], respectively, and the median t_{max} values of Laz were 2 hours after administration under fasting conditions and 3.5 to 4[38)] hours after administration with a high-fat meal.

Based on the above, the applicant explained that since food had no clear effects on the PK of Laz, Laz can be taken with or without food.

6.2.1.1.3 Effect of gastric pH on PK of Laz

According to an exploratory analysis using the PK data obtained from a foreign phase I/II study (Study NSC2001), coadministration with acid-reducing agents (proton pump inhibitors and H_2 receptor antagonists) had no clear effects on Laz exposure. Based on the above, the applicant explained that although the solubility of Laz decreases with increasing pH, an increase in gastric PH following coadministration with acid-reducing agents is unlikely to have a clinically relevant effect on the PK of Laz.

6.2.2 Clinical pharmacology

6.2.2.1 Global studies

6.2.2.1.1 Global[39)] phase I study (CTD 5.3.5.2.4, Study EDI1001 [Ami/Laz cohort] [ongoing since May 2016 (data cutoff date of November 15, 2022)])

An open-label, uncontrolled study was conducted in 108 patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously treated with chemotherapy (108 included in the PK analysis) to evaluate the PK etc. of Laz. Laz 240 mg QD was to be administered orally in combination with Ami,[40)] and plasma concentrations of Laz, serum concentrations of Ami, etc., were determined.

Table 22 and Table 23 show the PK parameters of Laz and Ami in patients treated with Laz and the proposed dosing regimen of Ami.

Table 22. PK parameters of Laz

Sampling day (Day)	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)
1	11	539 ± 151	2.02 (1.85, 4.12)	4,324 ± 1,419
22	15	573 ± 186	3.97 (0.93, 7.90)	7,341 ± 2,835

Mean ± SD, *Median (Min., Max.)

[38)] The median t_{max} values in Caucasian and Korean subjects were 3.5 and 4.0 hours, respectively.

[39)] Ami monotherapy cohorts etc. were conducted in Japan and overseas, and Ami/Laz cohort was conducted overseas.

[40)] The dosing regimens of Ami in (1) Part 1 and (2) Part 2 are shown below. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).
(1) Ami [(i) 700 mg for patients weighing <80 kg, 1,050 mg for patients weighing ≥80 kg or (ii) 1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg] was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles.
(2) Ami (1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg) was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles.

Table 23. PK parameters of Ami

Body weight	Dosing day	N	Pre-dose concentration (μg/mL)	C_{max} (μg/mL)	t_{max}*1 (h)	AUC*2 (μg·h/mL)
<80 kg	Cycle 1 Day 1	16	—	444 ± 95.3*3	—	37,365 ± 7,631
	Cycle 2 Day 1	14	295 ± 94.4	859 ± 297	4.31 (2.37, 25.4)	137,967 ± 36,267*4
	Cycle 4 Day 1	10	140 ± 57.4	642 ± 168	4.31 (2.32, 26.0)	91,073 ± 25,912*5
≥80 kg*6	Cycle 2 Day 1	11	285 ± 43.9	—	—	—
	Cycle 4 Day 1	11	163 ± 43.0	—	—	—

Mean ± SD; —, Not calculated;
*1 Median (Min., Max.), *2 AUC_{168h} on Cycle 1 Day1, AUC_{tau} in Cycle 2 onwards
*3 C_{max} after dosing on Day 2 because the first dose was split (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2)
*4 n = 13, *5 n = 9, *6 PK parameters on Cycle 1 Day1 were not calculated.

In 100 subjects assessed for anti-amivantamab antibodies after receiving amivantamab, no anti-amivantamab antibodies were detected.

6.2.2.1.2 Global[41] phase I/Ib study (CTD 5.3.5.2.1, Study NSC1001 (Japanese phase I part and Japanese phase Ib part [ongoing since September 2019 (data cutoff date of November 15, 2022)])

(1) Japanese phase I part (Laz monotherapy)

An open-label, uncontrolled study was conducted in 12 patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously treated with chemotherapy (12 included in the PK analysis) to evaluate the PK etc. of Laz. Laz 160, 240, or 320 mg QD was to be administered orally, and plasma concentrations of Laz, etc., were determined.

Table 24 shows the PK parameters of Laz. The accumulation ratio of Laz[42] following oral administration of Laz 240 mg QD was 3.05.

Table 24. PK parameters of Laz

Dosing regimen	Sampling day (Day)	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{24h} (ng·h/mL)
160 mg QD	1	3	560 ± 146	3.95 (1.87, 4.02)	3,887 ± 1,017
	22		675 ± 122	3.97 (1.95, 4.03)	9,727 ± 1,661
240 mg QD	1	5	451 ± 260	2.07 (1.98, 7.98)	3,360 ± 1,314
	22		568 ± 200	3.88 (1.97, 8.05)	9,293 ± 950*2
320 mg QD	1	3	853 ± 174	3.85 (1.93, 3.95)	7,976 ± 3,137
	22		1,760 ± 236	3.93 (3.92, 3.98)	27,684 ± 6,394

Mean ± SD, *1 Median (Min., Max.), *2 n = 4

(2) Japanese phase Ib part (Ami/Laz)

An open-label, uncontrolled study was conducted in 6 patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously treated with chemotherapy (6 included in the PK analysis) to evaluate the PK etc. of Laz. Laz 240 mg QD was to be administered orally in combination with Ami,[43] and plasma concentrations of Laz, etc., were determined.

[41] Japanese phase I part and Japanese phase Ib part were conducted in Japan, and Global phase Ib part was conducted in Japan and overseas.
[42] The ratio of AUC_{24h} on Day 22 to AUC_{24h} on Day 1
[43] Ami 1,050 or 1,400 mg, regardless of body weight, was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles. The first dose in Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).

Table 25 shows the PK parameters of Laz. The applicant explained that the plasma concentrations of Laz following administration of Ami/Laz showed a similar trend to the plasma concentrations of Laz following administration of Laz 240 mg alone in the monotherapy cohort.

Table 25. PK parameters of Laz

Dose of Ami (mg)	Sampling day (Day)	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)
1,050	1	3	408 ± 116	2.00 (1.00, 7.85)	4,256 ± 351
	22		612 ± 176	2.00 (1.02, 8.05)	7,226 ± 2803
1,400	1	3	608 ± 199	1.95 (1.90, 3.85)	5,446 ± 865
	22		694 ± 458	4.07 (3.97, 7.93)	7,727 ± 4,194

Mean ± SD, *Median (Min., Max.)

6.2.2.2 Foreign studies

6.2.2.2.1 Foreign phase I/II study (CTD 5.3.4.2.1, Study NSC2001 [ongoing since February 2017 (data cutoff date of January 8, 2021)])

An open-label, uncontrolled study was conducted in 181 patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC (176 included in the PK analysis) to evaluate the PK etc. of Laz. Laz 20 to 320 mg QD was to be administered orally, and plasma concentrations of Laz, etc., were determined.

Table 26 shows the PK parameters of Laz. The accumulation ratio of Laz [42] following oral administration of Laz 240 mg QD was 2.36. Steady-state Laz exposure was reached by Day 15.

Table 26. PK parameters of Laz

Dosing regimen	Sampling day (Day)	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)
20 mg QD	1	3	16.3 ± 9.68	1.97 (1.97, 4.00)	142 ± 53.1	17.5 ± 8.33
	22	3	31.8 ± 22.6	2.03 (1.05, 3.97)	347 ± 204	—
40 mg QD	1	6	43.5 ± 22.1	2.03 (2.02, 4.00)	362 ± 126	58.8 ± 29.8
	22	24	74.7 ± 34.7	2.04 (1.03, 10.1)	925 ± 374	—
80 mg QD	1	6	119 ± 45.0	2.04 (1.00, 6.03)	914 ± 259	79.6 ± 23.3
	22	19	187 ± 93.5	2.07 (1.00, 8.00)	2,430 ± 1,099	—
120 mg QD	1	6	204 ± 83.9	2.05 (1.02, 5.95)	1,517 ± 351	68.5 ± 21.1
	22	23	252 ± 116	2.05 (0.97, 6.07)	3,145 ± 1,341	—
160 mg QD	1	6	179 ± 60.9	4.09 (2.03, 10.2)	1,630 ± 430	59.9 ± 14.8
	22	15	361 ± 151	2.08 (1.05, 8.03)	4,814 ± 1,658	—
240 mg QD	1	4	434 ± 126	1.99 (1.98, 4.00)	2,866 ± 973	64.7 ± 21.2
	22	20	517 ± 222	2.06 (1.92, 6.17)	6,542 ± 3,227	—
320 mg QD	1	5	325 ± 156	2.00 (1.93, 2.17)	2,622 ± 701	101 ± 81.5
	22	4	614 ± 201	3.09 (2.03, 8.13)	7,880 ± 1,825	—

Mean ± SD, —, Not calculated, *Median (Min., Max.)

6.2.2.2.2 Foreign phase I study (CTD 5.3.3.1.1, Study NSC1004 [December 2020 to March 2021])

An open-label study was conducted in 8 healthy adult subjects (8 included in the PK analysis) to determine the mass balance of Laz. A single oral dose of ^{14}C-Laz 240 mg was to be administered, and radioactivity concentrations in plasma, urine, and feces, etc., were determined.

In the plasma collected up to 24 hours post-dose, unchanged Laz, M12 (a cysteinylglycine conjugate), M14 (a cysteine conjugate), and M15 (fused morpholino-benzimidazole with net loss of C_3H_6O) were mainly detected

and accounted for 41.0%, 23.6%, 12.3%, and 8.04% of the total radioactivity in plasma, respectively, in GSTM1 non-null patients and 49.3%, 19.6%, 9.06%, and 6.57% of the total radioactivity in plasma, respectively, in GSTM1 null patients.[44)]

Over 696 hours, 3.54% and 86.2% of the administered radioactivity were recovered in urine and feces, respectively. In the urine collected up to 48 hours post-dose and the feces collected up to 336 hours post-dose, unchanged Laz represented 0.13% and 5.04% of the administered radioactivity, respectively, in GSTM1 non-null patients and 0.18% and 2.50% of the administered radioactivity, respectively, in GSTM1 null patients. In feces, M14 was the major metabolite (13.9% and 11.9% of the administered radioactivity in GSTM1 non-null and null patients, respectively).

6.2.2.3 Drug interaction studies (CTD 5.3.3.4.1, Study NSC1003 [September 2020 to January 2021], CTD 5.3.3.4.2, Study NSC1008 [September 2021 to February 2022])

Table 27 and Table 28 show the results of clinical studies conducted to investigate pharmacokinetic interactions between Laz and concomitant drugs in healthy adult subjects.

Table 27. Effect of concomitant drug on PK of Laz (Evaluation of Laz as an object of interactions)

Study ID	Dosing regimen of Laz (Oral administration)	Concomitant drug	Dosing regimen of concomitant drug (Oral administration)	N (With/Without concomitant drug)	Geometric mean ratio [90% CI] (With/Without concomitant drug)	
					C_{max}	AUC_{last}
NSC1003	160 mg QD on Days 1 and 12	Itraconazole (Strong CYP3A inhibitor)	200 mg QD on Days 8-16	15/15	1.19 [1.08, 1.30]	1.46 [1.39, 1.53]
	240 mg QD on Days 1 and 19	Rifampicin (Strong CYP3A inducer)	600 mg QD on Days 8-22	16/16	0.282 [0.232, 0.343]	0.162 [0.138, 0.191]

Table 28. Effect of Laz on PK of concomitant drug (Evaluation of Laz as a precipitant of interactions)

Study ID	Dosing regimen of Laz (Oral administration)	Concomitant drug	Dosing regimen of concomitant drug (Oral administration)	N (With/Without Laz)	Geometric mean ratio [90% CI] (With/Without Laz)	
					C_{max}	AUC_{last}
NSC1008	160 mg QD on Days 5-14	Midazolam (CYP3A substrate)	2 mg QD on Days 1 and 13	19/19	1.39 [1.23, 1.58]	1.47 [1.34, 1.60]
		Rosuvastatin (BCRP substrate)	10 mg QD on Days 1 and 13	19/19*	2.24 [1.82, 2.76]	2.02 [1.70, 2.40]
		Metformin (OCT1 substrate)	500 mg QD on Days 1 and 13	19/19	0.809 [0.716, 0.913]	0.943 [0.835, 1.07]

*18/18 for AUC_{last}

6.2.2.4 Foreign phase I study to evaluate the effect of hepatic impairment on PK of Laz (CTD 5.3.3.3.1, Study NSC1007 [November 2021 to July 2022])

An open-label study was conducted in 8 healthy adult subjects and 8 patients with moderate (Child-Pugh class B) hepatic impairment (8 each included in the PK analysis) to evaluate the effect of hepatic impairment on the PK of Laz.[45)] A single oral dose of Laz 160 mg was to be administered in the fed state, and plasma concentrations of Laz were determined.

[44)] Given that GST M1-1 was shown to be mainly involved in the glutathione conjugation of Laz *in vitro* [see Section 4.2.3.1], the mass balance of Laz and the PK of Laz in GSTM1 non-null and null patients were determined.

[45)] Since moderate hepatic impairment had no clear effect on Laz exposure, Las was not studied in patients with mild or severe hepatic impairment.

The C_{max} and AUC_{inf} geometric mean ratios for patients with moderate hepatic impairment vs. healthy adult subjects [90% CI] were 0.796 [0.608, 1.04] and 1.03 [0.827, 1.29], respectively.

The fraction unbound in plasma of Laz from pre-dose to 6 hours post-dose was 0.57% to 1.08% in healthy adult subjects and 0.58% to 1.07% in patients with moderate hepatic impairment.

6.2.2.5 Use of Laz in patients with renal impairment

The effect of renal impairment on the PK of Laz has not been evaluated in a dedicated renal impairment study.

The applicant's explanation:
Given the following points etc., no dose adjustment of Laz is required in patients with renal impairment.

- The contribution of renal excretion to the clearance of Laz is small [see Section 6.2.2.2.2].
- Laz exposure by the degree of renal impairment was predicted from the PPK analysis [see Section 6.2.2.7]. The results are shown below.
  - The geometric mean ratios for the $C_{max,ss}$ of Laz following oral administration of Laz 240 mg QD for mild and moderate renal impairment (699 and 123 patients, respectively) vs. normal renal function [46)] (553 patients) were 1.03 [0.998, 1.06] and 1.04 [0.984, 1.10], respectively. The geometric mean ratios for the $AUC_{24h, ss}$ of Laz [90% CI] were 1.03 [0.993, 1.07] and 1.07 [1.01, 1.14], respectively.
- The incidence of adverse events by the degree of renal impairment in the Ami/Laz group of a global phase III study (MARIPOSA study) is shown below. There was no trend towards consistently increasing incidence of adverse events with decreasing renal function.
  - In patients with normal renal function [46)] (237 patients) and patients with mild or moderate renal impairment (263 and 20 patients, respectively), (1) the incidences of adverse events leading to death were 8.0%, 8.6%, and 5.0%, respectively. (2) The incidences of serious adverse events were 45.1%, 53.4%, and 55.0%, respectively. (3) The incidences of Grade ≥3 adverse events were 72.6%, 76.7%, and 90.0%, respectively. (4) The incidences of adverse events leading to discontinuation of Laz were 19.0%, 21.5%, and 25.0%, respectively. (5) The incidences of adverse events leading to dose interruption of Laz were 69.6%, 71.2%, and 85.0%, respectively. (6) The incidences of adverse events leading to dose reduction of Laz were 41.8%, 41.7%, and 45.0%, respectively.

6.2.2.6 Relationship between exposure and changes in QT/QTc interval

The relationship between plasma Laz concentration and ΔQTcP was analyzed using a linear mixed-effects model, based on the data from 243 patients who had time-matched PK/ECG data in a foreign phase I/II study (Study NSC2001). There was no clear relationship between plasma Laz concentration and ΔQTcP. The upper bound of the 90% confidence interval for the estimated ΔQTcP at the steady-state C_{max} (473 ng/mL) following oral administration of Laz 240 mg QD was 5.83 ms.

[46)] CrCL (mL/min) ≥90 was classified as normal renal function, CrCL ≥60 and <90 was classified as mild renal impairment, CrCL ≥30 and <60 was classified as moderate renal impairment, and CrCL ≥15 and <30 was classified as severe renal impairment.

Based on the above, the applicant explained that Laz administered at the proposed dosing regimen is unlikely to cause QT/QTc interval prolongation.

6.2.2.7 PPK analysis

Based on the Laz PK data obtained from a global phase I study (Study EDI1001), a global phase I/Ib study (Study NSC1001), a global phase III study (MARIPOSA study), a foreign phase I/II study (Study NSC2001), and a foreign phase III study (Study 301) (1,389 patients, 14,936 sampling points),[47] a PPK analysis was performed by non-linear mixed effects modeling (software used: NONMEM Version 7.4.3). The PK of Laz were described by a 2-compartment model with sequential zero- and first-order absorption.

In this analysis, using the base model incorporating the effects of body weight on the CL/F and V_2/F, body weight, age, creatinine clearance (CrCL), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sex, race, race (Japanese or non-Japanese), ethnicity, renal function,[46] hepatic function,[48] Eastern Cooperative Oncology Group performance status (ECOG PS), *EGFR* mutation type, cancer stage, prior treatment (naïve or non-naïve), brain metastasis, GSTM1 genotype, history of smoking, and combination therapy with Ami were tested as potential covariates on the CL/F and V_2/F. As significant covariates on (1) CL/F and (2) V_2/F, (1) sex, race (Japanese or non-Japanese), prior treatment (naïve or non-naïve), and GSTM1 genotype and (2) sex were identified.

The applicant's explanation about the above results:

- Since the effects of sex, race (Japanese or non-Japanese), and prior treatment (naïve or non-naïve) on Laz exposure were all limited,[49] these covariates are unlikely to have a clinically relevant impact on the PK of Laz.
- Although the Laz $C_{max,ss}$ and $AUC_{24h,\ ss}$ geometric mean ratios for GSTM1 non-null patients vs. GSTM1 null patients [90% CI] were estimated at 0.657 [0.631, 0.684] and 0.564 [0.539, 0.591], respectively, there was no clear relationship between Laz exposure and efficacy [see Section 6.2.2.8.1], and there were no clear differences in the incidence of adverse events between GSTM1 non-null and null patients.[50] Given these points, GSTM1 genotype is unlikely to have a clinically relevant impact on the

[47] For the patients included in the analysis, patient demographics [median (min., max.)] or the number of patients in each category are shown below. Body weight, 61.2 (28.5, 122) kg; age, 63 (21, 88) years; CrCL, 78.9 (19.8, 343) mL/min; albumin, 41 (21.0, 53.8) g/L; ALT, 17 (2.00, 163) U/L; AST, 21 (4.00, 97.0) U/L; ALP, 92 (19.0, 3.420) U/L; sex (525 men and 864 women); race (415 white patients, 931 Asian patients (including 89 Japanese patients), 43 patients with other race), ethnicity (81 Latino or Hispanic patients, 1,271 patients with other ethnicity, 37 patients with unknown ethnicity), renal function (556 patients with normal renal function, 706 patients with mild renal impairment, 124 patients with moderate renal impairment, 3 patients with severe renal impairment), hepatic function (1,245 patients with normal hepatic function, 142 patients with mild hepatic impairment, 2 patients with moderate hepatic impairment), ECOG PS (420 patients with grade 0, 969 patients with grade 1), *EGFR* mutation type (766 patients with Ex19del, 450 patients with L858R, 173 patients with other mutations), cancer stage (58 patients with grade I, 15 patients with grade II, 98 patients with grade III, 1,216 patients with grade IV, 2 patients with unknown grade), prior lines of therapy (0 in 658 patients, 1 in 193 patients, 2 in 242 patients, 3 in 141 patients, ≥4 in 155 patients), brain metastasis (Yes in 569 patients, No in 820 patients), GSTM1 genotype (257 non-null patients, 336 null patients, 796 patients with undetermined genotype), history of smoking (Yes in 479 patients, No in 890 patients, unknown in 20 patients), combination therapy with Ami (Yes in 932 patients, No in 457 patients)

[48] Classified by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

[49] The Laz $C_{max,ss}$ and $AUC_{24h,\ ss}$ geometric mean ratios for (1) male patients vs. female patients, (2) Japanese patients vs. non-Japanese patients, and (3) non-naïve patients vs. naïve patients were estimated at (1) 0.830 and 0.848, respectively, (2) 1.21 and 1.21, respectively, and (3) 0.917 and 0.886, respectively.

[50] In the Ami/Laz group of the MARIPOSA study, the incidences of (1) adverse events leading to death, (2) serious adverse events, (3) Grade ≥3 adverse events, (4) adverse events leading to discontinuation of Laz, (5) adverse events leading to dose interruption of Laz, and (6) adverse events leading to dose reduction of Laz in GSTM1 non-null and null patients were (1) 4.7% and 9.9%, respectively, (2) 43.8% and 53.4%, respectively, (3) 74.2% and 77.0%, respectively, (4) 15.6% and 23.6%, respectively, (5) 70.3% and 73.9%, respectively, and (6) 43.0% and 47.2%, respectively.

PK of Laz.

6.2.2.8 Exposure-efficacy/safety relationship

Based on the results from the Ami/Laz group in a global phase III study (MARIPOSA study), the relationships between Laz exposure and efficacy/safety were explored. Laz exposure was predicted from the PPK analysis [see Section 6.2.2.7].

6.2.2.8.1 Exposure-efficacy relationship

The relationship between Laz exposure (C_{avg} per day, C_{trough} and C_{avg} in Cycle 1, C_{avg} on Cycle 2 Day 1) and PFS was explored. There was no clear relationship between Laz exposure and PFS.

6.2.2.8.2 Exposure-safety relationship

The relationship between Laz exposure (the maximum C_{max} and C_{avg} in Cycle 1) and the incidence of ILD, paronychia, stomatitis, diarrhoea, paraesthesia, hypoalbuminaemia, rash of any grade, Grade ≥3 rash, venous thromboembolism of any grade, or Grade ≥3 venous thromboembolism was explored. (1) The incidence of stomatitis tended to increase with increasing the maximum C_{max} of Laz, and (2) the incidence of paraesthesia tended to increase with increasing C_{avg} in Cycle 1. Although the incidence of venous thromboembolism of any grade was lower in the first quartile group of the C_{avg} of Laz in Cycle 1 than in the second, third, and fourth quartile groups, there was no clear relationship among the second, third, and fourth quartile groups.

6.2.2.9 Differences in PK between Japanese and non-Japanese populations

The applicant's explanation:

Given the following point, there were no clear differences in the PK of Laz between Japanese and non-Japanese populations.

- In a global phase I/Ib study (Study NSC1001), a foreign phase I/II study (Study NSC2001), and the Ami/Laz group of a global phase III study (MARIPOSA study), there were no clear differences in the PK parameters of Laz following oral administration of Laz 240 mg QD between Japanese and non-Japanese patients (Table 29 and Table 30)

Table 29. PK parameters of Laz

Study ID	Sampling day (Day)	Study population	N	C_{max} (ng/mL)	t_{max} *1 (h)	AUC_{24h} (ng·h/mL)
NSC1001	1	Japanese patients	5	451 ± 260	2.07 (1.98, 7.98)	3,360 ± 1,314
	22		5	568 ± 200	3.88 (1.97, 8.05)	9,293 ± 950 *2
NSC2001	1	Non-Japanese patients	4	434 ± 126	1.99 (1.98, 4.00)	2,866 ± 973
	22		20	517 ± 222	2.06 (1.92, 6.17)	6,542 ± 3,227

Mean ± SD, *1 Median (Min., Max.), *2 N = 4

Table 30. PK parameters of Laz

Study ID	Sampling day (Day)	Study population	N	C_{trough} (ng/mL)
MARIPOSA	29	Japanese patients	24	231 ± 101
		Non-Japanese patients	293	231 ± 138
	57	Japanese patients	16	279 ± 133
		Non-Japanese patients	245	214 ± 125
	113	Japanese patients	12	235 ± 113
		Non-Japanese patients	216	220 ± 129

Mean ± SD

- In the PPK analysis, race (Japanese or non-Japanese) was identified as a significant covariate on the CL/F of Laz, but the effect of race on Laz exposure was limited [see Section 6.2.2.7].

6.R Outline of the review conducted by PMDA

PMDA's conclusion:

Based on the submitted data, the applicant's explanation about the clinical pharmacology etc. of Laz is acceptable, excluding the considerations in the following sections.

6.R.1 Use of Laz in patients with hepatic impairment

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

In a foreign phase I study (Study NSC1007) [see Section 6.2.2.4], there was no trend towards increased Laz exposure in patients with mild or moderate hepatic impairment than in healthy adult subjects. Thus, no dose adjustment of Laz is required in patients with mild, moderate, or severe hepatic impairment. Patients with severe hepatic impairment were not enrolled in a global phase III study (MARIPOSA study).

PMDA’s view:

PMDA accepted the applicant's explanation about the use of Laz in patients with mild or moderate hepatic impairment.

On the other hand, with regard to the use of Laz in patients with severe hepatic impairment, given that Laz is cleared primarily by hepatic metabolism [see Section 6.2.2.2.2], and that Laz safety information from patients with severe hepatic impairment is not available, the package insert should state that the blood concentration of Laz may rise in patients with severe hepatic impairment, and that Laz has not been studied in patients with severe hepatic impairment.

6.R.2 Pharmacokinetic interactions with CYP3A inhibitors or inducers

The applicant's explanation about concomitant use of Laz with CYP3A inhibitors or inducers:

(1) CYP3A inhibitors

Given the following points, concomitant use with CYP3A inhibitors is unlikely to have a clinically relevant effect on Laz exposure. Thus, a precautionary statement regarding concomitant use with CYP3A inhibitors is unnecessary.

- In a foreign phase I study (Study NSC1003), the Laz C_{max} and AUC_{inf} geometric mean ratios for Laz + itraconazole (a strong CYP3A inhibitor) vs. Laz alone were 1.19 and 1.46, respectively [see Section 6.2.2.3]. Meanwhile, the extent of increase in Laz exposure was within the inter-individual variability (C_{max}, 33.8%-41.1%; AUC_{inf}, 30.0%-52.1%) determined in foreign phase I studies (Study NSC1002, Study NSC1006, Study NSC1009).
- In the Ami/Laz group of the MARIPOSA study, there were no clear differences in the safety profile between patients receiving concomitant moderate CYP3A inhibitors and patients not receiving concomitant moderate CYP3A inhibitors.[51)]
- In accordance with "Drug interaction guideline for drug development and labeling recommendations" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018), assuming that the effect of a weak CYP3A inhibitor on the AUC_{last} of Laz is two-fifths of that of a strong CYP3A inhibitor, the Laz AUC_{last} geometric mean ratio for Laz + weak CYP3A inhibitor vs. Laz alone was predicted to be up to 1.18.

(2) CYP3A inducers

In Study NSC1003, the Laz C_{max} and AUC_{inf} geometric mean ratios for Laz + rifampicin (a strong CYP3A inducer) vs. Laz alone were 0.282 and 0.162, respectively [see Section 6.2.2.3]. Given the extent of decrease in Laz exposure when coadministered with rifampicin, coadministration with strong CYP3A inducers may decrease Laz exposure. Thus, the package insert will advise that caution is required when coadministering Laz with strong CYP3A inducers.

Since Laz is a substrate of CYP3A [see Section 4.2.3.1], and concomitant use with rifampicin (a strong CYP3A inducer) affected Laz exposure [see Section 6.2.2.3], the effect of a moderate CYP3A inducer on the PK of Laz was evaluated as follows, using a PBPK model.[52)]

Table 31 shows the predicted geometric mean ratios for the C_{max} and AUC_{tau} of Laz for Laz + CYP3A inducer vs. Laz alone.

[51)] In the Ami/Laz group of the MARIPOSA study, (1) the incidences of adverse events leading to death were 8.2% in patients not receiving concomitant CYP3A inhibitors or receiving concomitant weak CYP3A inhibitors and 7.1% in patients receiving concomitant moderate CYP3A inhibitors. (2) The incidences of serious adverse events were 47.5% and 55.4%, respectively. (3) The incidences of Grade ≥3 adverse events were 74.0% and 80.4%, respectively. (4) The incidences of adverse events leading to discontinuation of Laz were 21.8% and 12.5%, respectively. (5) The incidences of adverse events leading to dose interruption of Laz were 70.9% and 73.2%, respectively. (6) The incidences of adverse events leading to dose reduction of Laz were 41.8% and 39.3%, respectively.

[52)] The PBPK analysis was performed using Simcyp version 21. Laz absorption was modeled using a 1st order absorption model, and Laz distribution was modeled using the minimal PBPK model. The fractional contributions of (1) CYP3A and (2) GSTM1 to the metabolism of Laz, based on *in vivo* clearance obtained from foreign phase I studies (Studies 101, NSC1002, and NSC1003) and a foreign phase I/II study (Study NSC2001), were (1) 28% in GSTM1 non-null patients and 49% in GSTM1 null patients and (2) 32% in GSTM1 non-null patients. Simcyp default values were used for physiological parameters and CYP3A inducer-related parameters, and CYP3A inhibitor-related parameters were selected based on published literature (*Clin Pharmacokinet*. 2016; 55: 735-49).

Table 31. Effect of CYP3A inducer on PK of Laz

Concomitant drug	Observed or predicted value	GSTM1 genotype	Geometric mean ratio*1	
			C_{max}	AUC_{tau}*2
Rifampicin (strong CYP3A inducer)	Observed value*3	Non-null	0.28	0.18
		Null	0.28	0.15
	Predicted value*4	Non-null	0.56	0.42
		Null	0.44	0.27
Efavirenz (moderate CYP3A inducer)		Non-null	0.68	0.56
		Null	0.56	0.41

*1 Ratio for Laz + CYP3A inducer vs. Laz alone
*2 AUC_{120h} for observed values
*3 Results from Study NSC1003 [see Section 6.2.2.3]
*4 Predicted value at steady state following administration of Laz 240 mg QD in patients with cancer

There was a reasonable agreement between the above PBPK model-predicted values and the observed values obtained from clinical studies,[53)] for (i) Laz exposure and plasma concentration-time profiles following administration of Laz alone and (ii) the ratio of Laz exposure for Laz + itraconazole vs. Laz alone. On the other hand, since the predicted ratio of Laz exposure for Laz + rifampicin vs. Laz alone was higher than the observed value obtained from Study NSC1003 (Table 32), the above PBPK model seems to underpredict the CYP3A inducer effect of rifampicin.

Table 32. Effect of rifampicin on PK of Laz

GSTM1 genotype	C_{max} geometric mean ratio *1		AUC_{120h} geometric mean ratio*1	
	Predicated value*2	Observed value*3	Predicted value*2	Observed value*3
Non-null	0.58	0.28	0.43	0.18
Null	0.54	0.28	0.35	0.15

*1 Ratio for Laz + rifampicin vs. Laz alone
*2 Predicted value following a single dose of Laz 240 mg in healthy adult subjects
*3 Results from Study NSC1003 [see Section 6.2.2.3]

Based on the above results, the applicant's view on concomitant use of Laz with weak or moderate CYP3A inducers:

With regard to decreases in Laz exposure predicted from the above PBPK model, the PBPK model that underpredicted the CYP3A inducer effect of rifampicin was used, and the CYP3A inducer effect of efavirenz could therefore potentially also be underpredicted. However, given the following points, concomitant use with weak or moderate CYP3A inducers is unlikely to have a clinically relevant effect on Laz exposure. Thus, a precautionary statement regarding concomitant use with weak or moderate CYP3A inducers is unnecessary.

- In the Ami/Laz group of the MARIPOSA study, there was no clear relationship between Laz exposure and efficacy [see Section 6.2.2.8.1]
- In the Ami/Laz group of the MARIPOSA study, there was no trend towards clear differences in PFS between patients receiving concomitant weak or moderate CYP3A inducers[54)] and patients not receiving concomitant CYP3A inducers (Table 33).

[53)] (i) foreign phase I studies (Study 101, Study NSC1002, Study NSC1003, Study NSC1007, Study NSC1008) and a foreign phase I/II study (Study 201) (ii) Study NSC1003
[54)] The median times from the start of treatment with Laz to the start of coadministration with weak or moderate CYP3A inducers were 65 and 23 days, respectively, and the median durations of coadministration with weak or moderate CYP3A inducers were 15 and 42 days, respectively.

Table 33. Results of PFS as assessed by BICR in patients receiving concomitant weak or moderate CYP3A inducers and patients not receiving concomitant CYP3A inducers (MARIPOSA study)

	With moderate CYP3A inducers	With weak CYP3A inducers	Without CYP3A inducers
N	42	165	213
No. of events (%)	22 (52.4)	72 (43.6)	87 (40.8)
Median [95% CI] (months)	18.20 [14.42, －]	23.92 [18.43, －]	24.05 [20.11, －]

－, Not estimable

PMDA's discussion:

PMDA accepted the above explanation by the applicant concerning concomitant use with (1) weak or moderate CYP3A inhibitors and (2) weak or strong CYP3A inducers.

On the other hand, given the extent of increase in Laz exposure following coadministration of Laz with a strong CYP3A inhibitor, the possibility that coadministration with strong CYP3A inhibitors has a clinically relevant effect on Laz exposure cannot be ruled out. Thus, the package insert should advise that caution is required when coadministering Laz with strong CYP3A inhibitors.

Even when Laz exposure following coadministration with a moderate CYP3A inducer was predicted from the PBPK model that could potentially underpredict the effect of a CYP3A inducer, a certain extent of decrease in Laz exposure was predicted, and PFS in the Ami/Laz group of the MARIPOSA study tended to be shorter in patients receiving concomitant moderate CYP3A inducers than in patients not receiving concomitant CYP3A inducers (Table 33). Given these points, the package insert should advise that concomitant use with moderate CYP3A inducers should be avoided wherever possible, and that an alternate concomitant medication with no potential to induce CYP3A or the potential to weakly induce CYP3A should be considered.

Since the information on CYP3A-mediated pharmacokinetic interactions of Laz is important for assessing the appropriateness of precautionary statements regarding concomitant use with CYP3A inhibitors or inducers, information collection should be continued, and if a new finding becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

6.R.3 Pharmacokinetic interactions with CYP3A, BCRP, or OCT1 substrates

The applicant's explanation about concomitant use of Laz with (1) CYP3A or BCRP substrates or (2) OCT1 substrates:

(1) CYP3A substrate (midazolam) or BCRP substrate (rosuvastatin)

In a foreign phase I study (Study NSC1008), the midazolam and rosuvastatin AUC_{last} geometric mean ratios for midazolam or rosuvastatin + Laz vs. midazolam or rosuvastatin alone were 1.47 and 2.02, respectively [see Section 6.2.2.3]. Given the extent of increase in midazolam or rosuvastatin exposure following coadministration with Laz, caution is required when coadministering Laz with CYP3A or BCRP substrates with a narrow therapeutic window. Thus, the relevant precautionary statement will be included in the package insert. On the other hand, a precautionary statement regarding concomitant use with other CYP3A or BCRP

substrates is unnecessary because the extent of increase in exposure to these substrates is unlikely to have a clinically relevant effect.

(2) OCT1 substrate (metformin)
In a foreign phase I study (Study NSC1008), the metformin AUC_{last} geometric mean ratio for metformin + Laz vs. metformin alone was 0.943 [see Section 6.2.2.3]. A precautionary statement regarding concomitant use with OCT1 substrates is unnecessary because coadministration with Laz is unlikely to have a clinically meaningful effect on OCT1 substrate exposure.

PMDA's view:
PMDA accepted the above explanation by the applicant concerning concomitant use of Laz with OCT1 substrates.

On the other hand, given the extent of increase in midazolam or rosuvastatin exposure following coadministration with Laz [see Section 6.2.2.3], the possibility that Laz has a clinically relevant effect on the exposure to CYP3A or BCRP substrates, regardless of the width of their therapeutic windows, cannot be ruled out, etc. Thus, the package insert should advise that caution is required when coadministering Laz with CYP3A or BCRP substrates, regardless of the width of their therapeutic windows.

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 the results from the studies presented in Table 34.

Table 34. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global[*1]	EDI1001[*2]	I	Patients with unresectable advanced or recurrent NSCLC	[Ami monotherapy cohorts] Part 1: 80 Part 2: 409	[Part 1] Ami administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles. Dose escalation was to progress from 140 mg to 350, 700,[*3] 1,050,[*3] 1,400,[*3] and 1,750[*3] mg. [Part 2] Ami[*3, 4] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles.	Tolerability Safety Efficacy PK
					[Ami/Laz cohort] Part 1: 63 Part 2: 45	[Part 1] Ami[*3, 5] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally [Part 2] Ami[*3, 4] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally	
		NSC1001	I/Ib	Patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	[Japanese phase I part] 12 [Japanese phase Ib part] 6 [Ami/Laz cohort A of Global phase Ib part] 162	[Japanese phase I part] Laz 160, 240, or 320 mg QD orally [Japanese phase Ib part] Ami[*3] 1,050 or 1,400 mg, regardless of body weight, administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally	Tolerability Safety Efficacy PK

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
						[Ami/Laz cohort A of Global phase Ib part] Ami[*3, 6] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally	
		MARIPOSA	III	Patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy	1,074 (1) 429 (2) 429 (3) 216	(1) Ami[*3, 6] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally (2) Osi 80 mg QD orally, in combination with placebo (3) Laz 240 mg QD orally, in combination with placebo	Efficacy Safety
Reference	Foreign	101	I	Healthy adult subjects	24	A single oral dose of Laz 240 mg under fasting conditions or after a high-fat meal	PK
		NSC1002	I	Healthy adult subjects	48	A single oral dose of Laz 240 mg (Formulations manufactured at clinical scale or at commercial scale)	PK
		NSC1003	I	Healthy adult subjects	32	Cohort 1: Laz 160 mg QD orally in fed state on Days 1 and 12, with itraconazole 200 mg QD orally in fed state on Days 8-16 Cohort 2: Laz 240 mg QD orally in fasted state on Days 1 and 19, with rifampicin 600 mg QD orally in fasted state on Days 8-22	PK
		NSC1004	I	Healthy adult subjects	8	A single oral dose of Laz 240 mg (capsules containing ^{14}C-labeled and unlabeled Laz)	PK
		NSC1006	I	Healthy adult subjects	18	A single oral dose of Laz 240 mg (G002 formulation, G004 formulation, or G005 formulation)	PK
		NSC1007	I	Adult subjects with hepatic impairment and healthy adult subjects	16	A single oral dose of Laz 160 mg	PK
		NSC1008	I	Healthy adult subjects	20	(1) Laz 160 mg QD orally (2) Midazolam 2 mg QD orally, rosuvastatin 10 mg QD orally, or metformin 500 mg QD orally (2) in fasted state on Day 1, (1) in fed state on Days 5-12, (1) and (2) in fasted state on Day 13, and (1) in fed state on Day 14	PK
		NSC1009	I	Healthy adult subjects	64	A single oral dose of Laz 240 mg (G001 formulation, G002 formulation, G004 formulation, or G005 formulation)	PK
		NSC2001	I/II	Patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	Part A: 38 Part B: 89 Part C: 97 Part D: 28	Laz QD administered orally at the following doses in 3-week cycles Part A: 20, 40, 80, 120, 160, 240, or 320 mg Part B: 40, 80, 120, 160, or 240 mg Part C: 240 mg Part D: 240 or 320 mg	Tolerability Safety Efficacy PK
		301	III	Patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy	393 (1) 196 (2) 197	(1) Laz 240 mg and placebo QD orally (2) Gefitinib 250 mg and placebo QD orally	Efficacy Safety

*1 Ami monotherapy cohorts etc. were conducted in Japan and overseas. Ami/Laz cohort was conducted overseas. *2 The study consisted of (1) Ami monotherapy cohorts, (2) Ami/Laz cohort, and (3) Ami/CP cohort, and (1) and (2) were submitted in the present application. *3 The first dose in Cycle 1 was split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2). *4 1,050 mg for patients weighing <80 kg and 1,400 mg for patients weighing ≥80 kg, *5 (1) 700 mg for patients weighing <80 kg and 1,050 mg for patients weighing ≥80 kg or (2) 1,050 mg for patients weighing <80 kg and 1,400 mg for patients weighing ≥80 kg, *6 1,050 mg for patients weighing <80 kg and 1,400 mg for patients weighing ≥80 kg

The clinical studies are summarized below. Among the data submitted for safety evaluation, the main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies." The study results on PK are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology." Since the data from Ami monotherapy cohorts in Study EDI1001 were submitted and previously evaluated for the initial approval of Ami (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024"), these results are omitted.

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global[39] phase I study (CTD5.3.5.2.4, Study EDI1001 [Ami/Laz cohort] [ongoing since May 2016 (data cutoff date of November 15, 2022)])

An open-label, uncontrolled study was conducted to evaluate the tolerability, safety, efficacy, etc., of Ami/Laz in patients with *EGFR* mutation-positive[55] unresectable advanced or recurrent NSCLC previously treated with chemotherapy (target sample size, 6 subjects at each dose level in Part 1, up to 100 subjects in Part 2). Part 1 was conducted at 12 sites overseas, and Part 2 was conducted at 28 sites overseas.

The dosing regimens are shown in the table below. Treatment was to continue until disease progression or any criterion for treatment discontinuation was met.

Part 1	Ami [(1) 700 mg for patients weighing <80 kg, 1,050 mg for patients weighing ≥80 kg or (2) 1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg] was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).
Part 2	Ami (1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg) was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).

All of 108 subjects enrolled in the Ami/Laz cohort (63 in Part 1, 45 in Part 2) received study drug and were included in the safety analysis set.

In Part 1 of Ami/Laz cohort, the dose-limiting toxicity (DLT) evaluation period lasted until 28 days after the start of Ami/Laz treatment. No DLTs were observed, and the recommended phase II dose (RP2D) of Ami in combination with Laz 240 mg QD orally was determined to be 1,050 mg for patients weighing <80 kg or 1,400 mg for patients weighing ≥80 kg, administered intravenously QW in Cycle 1 and quaque 2 weeks or twice weekly (Q2W) for subsequent cycles.

Regarding safety, 3 of 52 subjects (5.8%) in Part 1 and 5 of 45 subjects (11.1%) in Part 2 died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than progressive disease (3 subjects in Part 1, 1 subject in Part 2) were pneumonia; back pain; respiratory distress; and others

[55] Patients diagnosed with Ex19del or L858R mutation were enrolled.

(lung adenocarcinoma and pneumonitis) (1 subject each) in Part 2, and a causal relationship to Ami/Laz was denied for all causes of deaths classified as adverse events.[56)]

7.1.1.2 Global phase I/Ib study (CTD5.3.5.2.1, Study NSC1001 (Japanese phase I part, Japanese phase Ib part, Ami/Laz cohort A of Global phase Ib part) [ongoing since September 2019 (data cutoff date of November 15, 2022)])

An open-label, uncontrolled study (Japanese phase I part, Japanese phase Ib part, Ami/Laz cohort A of Global phase Ib part) was conducted to evaluate the tolerability, safety, efficacy, etc., of Laz monotherapy, Ami/Laz, etc., in patients with *EGFR* mutation-positive[57)] unresectable advanced or recurrent NSCLC previously treated with chemotherapy. The dosing regimens are shown in the table below, and treatment was to continue until disease progression or any criterion for treatment discontinuation was met.

Japanese phase I part	Laz 160, 240, or 320 mg QD orally
Japanese phase Ib part	Ami 1,050 or 1,400 mg, regardless of body weight, was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).
Ami/Laz cohort A of Global phase Ib part	Ami (1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg) was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).

All of 180 subjects enrolled in the study (12 in Japanese phase I part, 6 in Japanese phase Ib part, 162 in Ami/Laz cohort A of Global phase Ib part) received study drug and were included in the safety analysis set (including 27 Japanese patients in Ami/Laz cohort A of Global phase Ib part).

In Japanese phase I part of the study, the DLT evaluation period lasted until 21 days after the start of Laz treatment. Given that no DLTs were observed, and taking account of the dose that can achieve the target plasma concentration for the efficacy of Laz,[58)] the RP2D of Laz monotherapy was determined to be 240 mg QD. In Japanese phase Ib part of the study, the DLT evaluation period lasted until 28 days after the start of Ami/Laz treatment. No DLTs were observed.

Regarding safety, no deaths occurred during the study treatment period or within 30 days after the last dose of study drug in Japanese phase I part and Japanese phase Ib part, and 28 of 162 subjects (17.3%) (including 3 Japanese patients) died during the study treatment period or within 30 days after the last dose of study drug in Ami/Laz cohort A of Global phase Ib part. The causes of deaths other than progressive disease (24 patients including 3 Japanese patients) were acute respiratory failure; respiratory distress; pneumonia; and COVID-19 (1 patient each), and a causal relationship to study drug was denied for all those events.

[56)] The causes of deaths were classified as "adverse events," "progressive disease," or "others." For the causes of deaths classified as "adverse events," the causal relationship to study drug was assessed.

[57)] (1) Patients with an *EGFR* mutation, as detected by testing performed by a certified or accredited local laboratory were enrolled in Japanese phase I part and Japanese phase Ib part, and (2) patients with Ex19del or L858R mutations, as detected by testing performed by a certified or accredited local laboratory were enrolled in Ami/Laz cohort A of Global phase Ib part.

[58)] Based on the data obtained from a foreign phase I/II study (Study NSC2001), the relationship between Laz exposure (the steady-state C_{trough}) and PFS was explored. Since PFS tended to be shorter in the first quartile (Q1) of the steady state C_{trough}, the target plasma concentration to achieve favorable efficacy was set to the second quartile of the C_{trough} (the 5th and 95th percentiles of Q2 exposure were 58.6 and 111 ng/mL, respectively).

7.1.1.3 Global phase III study (CTD5.3.5.1.1, MARIPOSA study [ongoing since October 2020 (data cutoff date of August 11, 2023)])

A randomized, partial-blind[59] study was conducted at 262 sites in 27 countries or regions including Japan to compare the efficacy and safety of Ami/Laz versus Osi in patients with *EGFR* mutation-positive[60] unresectable advanced or recurrent NSCLC previously untreated with chemotherapy (target sample size, approximately 1,000 subjects[61]).

The dosing regimens are shown in the table below. Treatment was to continue until disease progression or any criterion for treatment discontinuation was met.

Ami/Laz group	Ami (1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg) was to be administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with Laz 240 mg QD orally. The first dose of Cycle 1 was to be split over 2 days (350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2).
Osi group	Osi 80 mg QD orally in combination with placebo
Laz group	Laz 240 mg QD orally in combination with placebo

All of 1,074 subjects who were enrolled in the study and randomized (429 in the Ami/Laz group, 429 in the Osi group, 216 in the Laz group) were included in the full analysis set (FAS), which was used as the efficacy population (including 29 Japanese patients in the Ami/Laz group, 32 Japanese patients in the Osi group, and 17 Japanese patients in the Laz group). After excluding 12 subjects who did not receive study drug (8 in the Ami/Laz group, 1 in the Osi group, 3 in the Laz group), 1,062 subjects (421 in the Ami/Laz group, 428 in the Osi group, 213 in the Laz group) were included in the safety analysis set (including 29 Japanese patients in the Ami/Laz group, 32 Japanese patients in the Osi group, and 16 Japanese patients in the Laz group).

The primary endpoint for the study was PFS[62] as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 for the Ami/Laz group compared to the Osi group. When (1) approximately 120 PFS events, (2) approximately 280 PFS events, and (3) approximately 450 PFS events (in the Ami/Laz and Osi groups combined) had been observed, (1) an interim analysis for futility, (2) an interim analysis for efficacy assessment, and (3) the final analysis were to be conducted. The Lan-DeMets O'Brien-Fleming α-spending function was to be used to control the type I error rate for the interim analyses.

Regarding efficacy, the results of the final analysis of the primary endpoint of PFS as assessed by BICR (data cutoff date of August 11, 2023) and the Kaplan-Meier curves are shown in Table 35 and Figure 4, respectively.

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[59] Randomization to Osi or Laz in a double-blind fashion, and randomization to Ami/Laz in an open-label fashion.

[60] Patients with Ex19del or L858R mutations, as detected by testing performed by a certified or accredited local laboratory were included in the study.

[61] For the primary endpoint of PFS as assessed by BICR, assuming a median PFS of 26 months in the Ami/Laz group and 19 months in the Osi group, a total of 450 PFS events were required to detect a hazard ratio of 0.73 with approximately 90% power at a two-sided level of significance of 0.05. Taking account of the randomization ratio across the Ami/Laz, Osi, and Laz groups (2:2:1), the dropout rate, etc., a sample size was chosen.

[62] PFS was defined as the time from randomization until (1) the date of objective disease progression based on BICR using RECIST v1.1 or (2) death (by any cause), whichever came first, regardless of whether or not study treatment was continued or whether or not subsequent therapy was started. The following patients were to be censored at the specified time points.

- Patients who had not progressed or had not died, patients who had been lost to follow-up, and patients who had withdrawn their consent were to be censored at their last imaging assessment date.
- Patients who had progressed or had died after 2 or more consecutive (1) missed imaging assessments or (2) unevaluable imaging assessments were to be censored at their last evaluable imaging assessment date.
- Patients who had no evaluable baseline or post-baseline disease assessment were to be censored at the date of randomization.

The superiority of Ami/Laz over Osi was demonstrated.[63)]

Table 35. Results of final analysis of PFS (BICR, FAS, data cutoff date of August 11, 2023)

	Ami/Laz	Osi
N	429	429
No. of events (%)	192 (44.8)	252 (58.7)
Median [95% CI] (months)	23.72 [19.12, 27.66]	16.59 [14.78, 18.46]
Hazard ratio [95% CI]*1	0.70 [0.58, 0.85]	
P-value (two-sided)*2	0.0002	

*1 A Cox proportional-hazards model stratified by *EGFR* mutation type (Ex19del, L858R), race (Asian, non-Asian), and history of brain metastasis (yes, no)
*2 Stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model), a significance level (two-sided) of 0.05

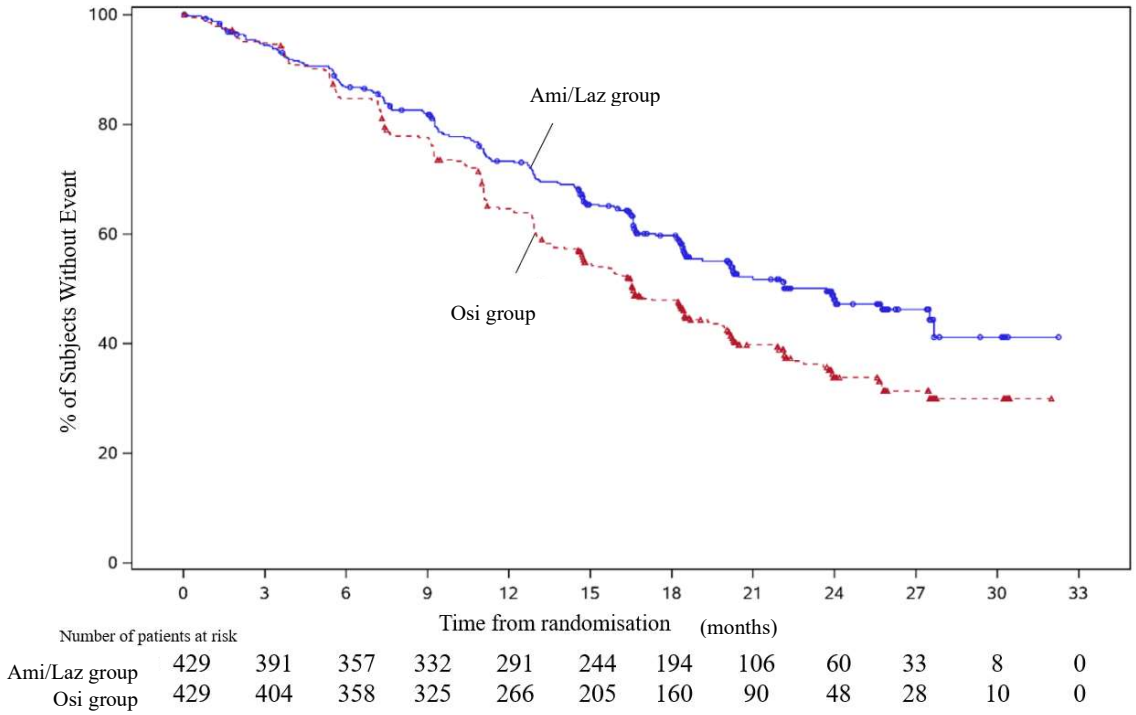

Figure 4. Kaplan-Meier curves of PFS at the time of final analysis (BICR, FAS, data cutoff date of August 11, 2023)

Regarding safety, 40 of 421 subjects (9.5%) in the Ami/Laz group, 45 of 428 subjects (10.5%) in the Osi group, and 20 of 213 subjects (9.4%) in the Laz group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than progressive disease (6 subjects in the Ami/Laz group, 18 subjects in the Osi group, 7 subjects in the Laz group) were pneumonia; respiratory failure; and sudden death (4 subjects each); death (3 subjects); myocardial infarction; septic shock; and pulmonary embolism (2 subjects each); and acinetobacter sepsis; COVID-19; COVID-19 pneumonia; urosepsis; acute respiratory distress syndrome; pneumonitis; coronary artery disease, myocardial infarction, and myocardial rupture; coronary artery arteriosclerosis and pneumonia; cardiopulmonary failure; cerebral infarction; ischaemic cerebral infarction; circulatory collapse; and others (unknown[64)]) (1 subject each) in the Ami/Laz group,

[63)] The IDMC notified the applicant that the efficacy stopping criteria had been met for PFS at the time of PFS interim analysis (data cutoff date of January 15, 2023). However, taking into account that the median duration of follow-up was rather short at 15.1 months, the applicant decided to maintain the blinding until the final analysis of PFS. Since the efficacy stopping criteria had been met at the time of this interim analysis, a two-sided alpha level of 0.05 was to be used for the final analysis of PFS. The hazard ratio of PFS [95% CI] at the interim analysis was 0.75 [0.60, 0.93] (*P* = 0.0097 [stratified log-rank test, a two-sided significance level of 0.0159]).
[64)] The cause of death was not identified.

pneumonia (4 subjects); COVID-19 (3 subjects); respiratory failure; ILD; and death (2 subjects each); and pneumonia aspiration; dyspnoea; hydrothorax; ketoacidosis; cerebral haemorrhage; haemoptysis; cerebrovascular accident; sudden death; metabolic acidosis; lower respiratory tract infection; sepsis; respiratory tract infection and septic shock; cardiac failure; and pulmonary embolism (1 subject each) in the Osi group, and pneumonia (3 subjects); pulmonary embolism; and cardiac arrest (2 subjects each); and sudden death; respiratory tract infection; respiratory failure; cerebrovascular accident; death; and others (unknown[64)]) (1 subject each) in the Laz group. As to the causes of deaths classified as adverse events,[56)] a causal relationship to study drug could not be ruled out for coronary artery disease and myocardial infarction; pneumonitis; myocardial infarction; and sudden death (1 subject each) in the Ami/Laz group, ILD (2 subjects) in the Osi group, and cerebrovascular accident (1 subject) in the Laz group.

One Japanese patient in the Ami/Laz group and 1 Japanese patient in the Osi group died during the study treatment period or within 30 days after the last dose of study drug, but no Japanese patients in the Laz group died. The cause of death other than progressive disease (1 Japanese patient in the Osi group) was cerebral infarction (1 Japanese patient) in the Ami/Laz group, and its causal relationship to study drug was denied.

7.2 Reference data

7.2.1 Clinical pharmacology studies

In 8 clinical pharmacology studies (Study 101, Study NSC1002, Study NSC1006, Study NSC1009, Study NSC1004, Study NSC1007, Study NSC1003, Study NSC1008 [see Table 34]), 1 of 48 subjects (2.1%) in Study NSC1002 died (completed suicide) during the study treatment period or within 30 days after the last dose of study drug, and its causal relationship to study drug was denied.

7.2.2 Foreign studies

7.2.2.1 Foreign phase I/II study (CTD5.3.4.2.1-1, Study NSC2001 [ongoing since February 2017 (data cutoff date of January 8, 2021)])

Regarding safety, deaths occurring during the study treatment period or within 30 days after the last dose of study drug in each part are shown in the table below.

Part A	One of 6 subjects (16.7%) in the 80 mg cohort and 2 of 6 subjects (33.3%) in the 160 mg cohort died. The cause of death other than progressive disease (1 subject each in the 80 mg and 160 mg cohorts) was cardiac arrest (1 subject) in the 160 mg cohort, and its causal relationship to study drug was denied.
Part B	One of 20 subjects (5.0%) in the 40 mg cohort and 1 of 14 subjects (7.1%) in the 80 mg cohort died. The cause of death other than progressive disease (1 subject in the 40 mg cohort) was pulmonary embolism (1 subject) in the 80 mg cohort, and its causal relationship to study drug was denied.
Part C	Five of 97 subjects (5.2%) died. The causes of deaths other than progressive disease (2 subjects) were pneumonia; pulmonary thromboembolism; and worsening of dyspnoea (1 subject each), and a causal relationship to study drug was denied for all those events.
Part D	One of 15 subjects (6.7%) in the 240 mg cohort and 2 of 13 subjects (15.4%) in the 320 mg cohort died. The cause of death other than progressive disease (1 subject each in the 240 mg and 320 mg cohorts) was pulmonary thromboembolism (1 subject) in the 320 mg cohort, and its causal relationship to study drug was denied.

7.2.2.2 Foreign phase III study (CTD5.3.5.1.2, Study 301 [ongoing since February 2020 (data cutoff date of July 29, 2022)])

Regarding safety, 19 of 196 subjects (9.7%) in the Laz group and 28 of 197 subjects (14.2%) in the gefitinib group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than progressive disease (7 subjects in the Laz group, 19 subjects in the gefitinib group) were pneumonia; pneumonia aspiration; sepsis; septic shock; ILD; respiratory failure; and malignant neoplasm of unknown primary site (1 subject each); unknown (4 subjects), and others (suicide) (1 subject) in the Laz group and pneumonia; pneumocystis jirovecii pneumonia; suspected COVID-19; aspiration; and pulmonary embolism (1 subject each); and unknown (4 subjects) in the gefitinib group. A causal relationship to Laz could not be ruled out for 1 case of ILD in the Laz group.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

Regarding the efficacy and safety of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy, PMDA decided to focus its review on the MARIPOSA study. Its efficacy in Japanese patients is evaluated systematically based on the MARIPOSA study etc., in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), partial revision of "Basic Principles on Global Clinical Trials (Reference Cases)"(MHLW/PSEHB/PED Administrative Notice dated December 10, 2021), "Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that the efficacy of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy was demonstrated.

7.R.2.1 Choice of control group

The applicant's explanation about the choice of a control group for the MARIPOSA study:

At the time of planning the MARIPOSA study, the Japanese and foreign clinical practice guidelines (the Japanese clinical practice guideline [2019], National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer [NCCN guidelines (NSCLC)] [v.2.2018], etc.) recommended Osi for patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy. Thus, Osi was selected as the comparator in the MARIPOSA study.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint

The applicant's explanation about selection of the primary endpoint for the MARIPOSA study:

In patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy, longer PFS was expected to delay worsening of clinical symptoms associated with disease progression, etc., and was considered clinically meaningful. Thus, PFS was selected as the primary endpoint for the MARIPOSA study.

PMDA's view:
Although the above explanation by the applicant (longer PFS in the patient population of the MARIPOSA study is clinically meaningful to a certain extent) is understandable, given that these patients are treated with an expectation of survival benefit, etc., PMDA will also review the results of overall survival (OS) at the time of regulatory review.

7.R.2.3 Results of efficacy assessment

The MARIPOSA study demonstrated the superiority of Ami/Laz over Osi in the primary endpoint of PFS as assessed by BICR [see Section 7.1.1.3].

In the MARIPOSA study, if the superiority of Ami/Laz over Osi in PFS was demonstrated, a secondary endpoint of OS was to be tested. An interim analysis of OS was to be conducted at the time of the final analysis of PFS. The final analysis of OS was to be conducted when a total of approximately 390 OS events in the Ami/Laz and Osi groups combined had been observed. The Lan-DeMets O'Brien-Fleming α-spending function was to be used to control the type I error rate for the interim analysis.

The results of the interim analysis of OS (data cutoff date of August 11, 2023) and the Kaplan-Meier curves in the MARIPOSA study are shown in Table 36 and Figure 5, respectively. The incidence of deaths within 6 months after randomization[65)] was higher in the Ami/Laz group than in the Osi group, and the causes of these deaths (29 in the Ami/Laz group, 19 in the Osi group) were progressive disease (5 subjects) and adverse events (24 subjects) (sudden death [4 subjects]; death [3 subjects]; pneumonia; pneumonitis; and respiratory failure [2 subjects each]; and acinetobacter sepsis; acute respiratory distress syndrome; cerebral infarction; septic shock; hypersensitivity pneumonitis; COVID-19; bone marrow failure; coronary artery arteriosclerosis and pneumonia; cardiopulmonary failure; pulmonary embolism; and COVID-19 pneumonia [1 subject each]) in the Ami/Laz group and progressive disease (4 subjects), adverse events (14 subjects) (pneumonia [2 subjects]; and dyspnoea; hydrothorax; brain oedema and cerebral haemorrhage; ILD; respiratory failure; sudden death; metabolic acidosis; lower respiratory tract infection; COVID-19; sepsis; respiratory tract infection and septic shock; and cardiac failure [1 subject each]), and others (COVID-19-related[66)]) (1 subject) in the Osi group. A causal relationship to study drug could not be ruled out for pneumonitis (2 subjects); and sudden death; hypersensitivity pneumonitis; and bone marrow failure (1 subject each) in the Ami/Laz group and ILD (1 subject) in the Osi group.

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65) The incidences of deaths (%) (1) within 3 months, (2) at >3 to 6 months, (3) at >6 to 9 months, and (4) at >9 to 12 months after randomization in the Ami/Laz and Osi groups were (1) 4.0% and 2.8%, respectively, (2) 3.0% and 1.6%, respectively, (3) 1.6% and 2.6%, respectively, and (4) 1.6% and 4.7%, respectively.

66) Although the subject died due to an adverse event, as the event occurred outside the adverse event reporting period in the MARIPOSA study (through 30 days after the last dose of study drug), and its causal relationship to study drug was denied, the cause of death was reported as "others."

Table 36. Results of interim analysis of OS (FAS, data cutoff date of August 11, 2023)

	Ami/Laz	Osi
N	429	429
No. of events (%)	97 (22.6)	117 (27.3)
Median [95% CI] (months)	－ [－, －]	－ [－, －]
Hazard ratio [95% CI][*1, 2]	0.80 [0.61, 1.05]	
P-value (two-sided)[*3]	0.1099	

－, Not estimable

*1 A Cox proportional-hazards model stratified by *EGFR* mutation type (Ex19del, L858R), race (Asian, non-Asian), and history of brain metastasis (yes, no)

*2 The 99.5% CI corresponding to the significance level was [0.55, 1.18].

*3 Stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model), a significance level (two-sided) of 0.005

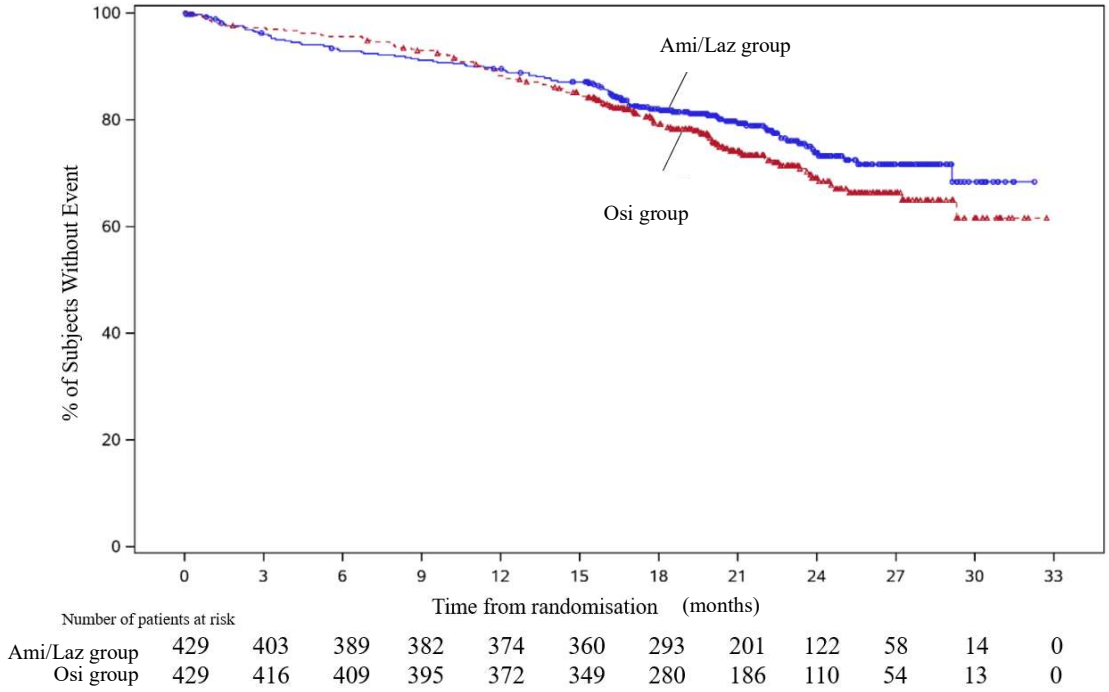

Figure 5. Kaplan-Meier curves of OS at the time of interim analysis (FAS, data cutoff date of August 11, 2023)

The results of an exploratory ad hoc analysis of OS (data cutoff date of May 13, 2024), which was requested by a foreign regulatory authority, and the Kaplan-Meier curves are shown in Table 37 and Figure 6, respectively.

Table 37. Results of additional ad hoc analysis of OS (FAS, data cutoff date of May 13, 2024)

	Ami/Laz	Osi
N	429	429
No. of events (%)	142 (33.1)	177 (41.3)
Median [95% CI] (months)	－ [－, －]	37.32 [32.53, －]
Hazard ratio [95% CI][*]	0.77 [0.61, 0.96]	

－, Not estimable

* A Cox proportional-hazards model stratified by *EGFR* mutation type (Ex19del, L858R), race (Asian, non-Asian), and history of brain metastasis (yes, no)

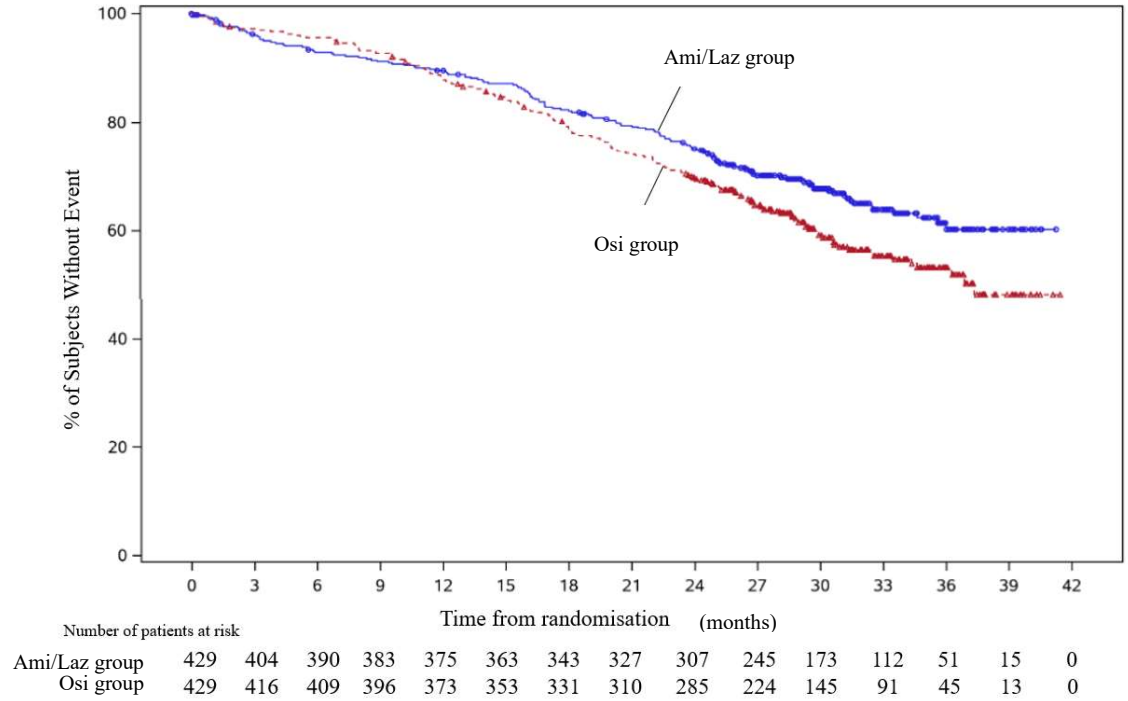

Figure 6. Kaplan-Meier curves of OS at the time of additional ad hoc analysis (FAS, data cutoff date of May 13, 2024)

In addition, the results of efficacy analyses in the Ami/Laz and Laz groups, which were pre-planned to determine the clinical significance of adding Ami to Laz in the MARIPOSA study, are shown in Table 38 and Figure 7.

Table 38. Results of final analysis of PFS and interim analysis of OS in Ami/Laz and Laz groups (BICR, FAS, data cutoff date of August 11, 2023)

	PFS		OS	
	Ami/Laz	Laz	Ami/Laz	Laz
N	429	216	429	216
No. of events (%)	192 (44.8)	121 (56.0)	97 (22.6)	56 (25.9)
Median [95% CI] (months)	23.72 [19.12, 27.66]	18.46 [14.75, 20.11]	－ [－, －]	－ [－, －]
Hazard ratio [95% CI]*	0.72 [0.57, 0.90]		0.82 [0.59, 1.14]	

－, Not estimable

* A Cox proportional-hazards model stratified by *EGFR* mutation type (Ex19del, L858R), race (Asian, non-Asian), and history of brain metastasis (yes, no)

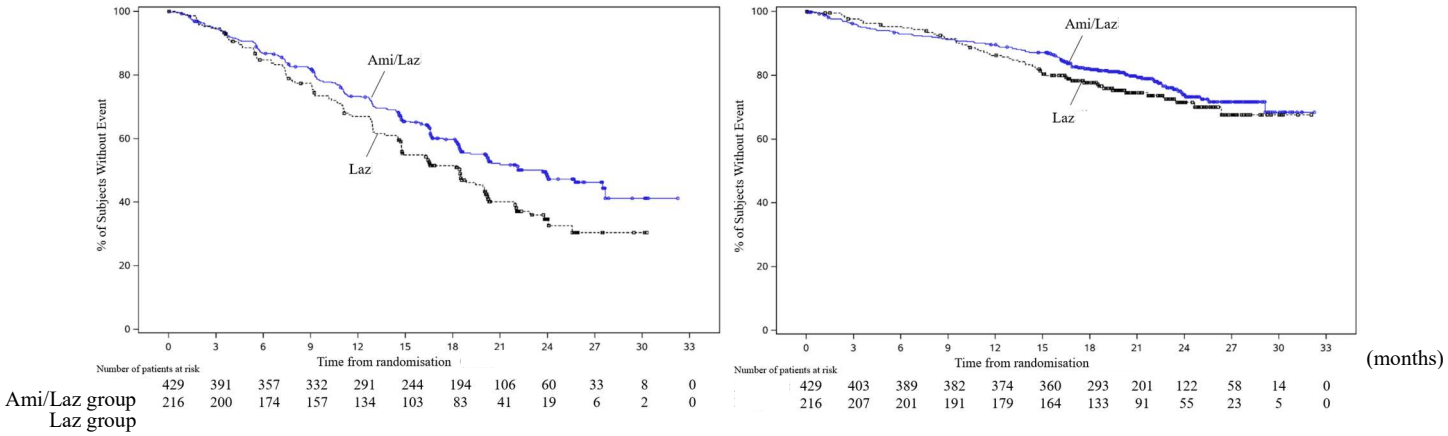

Figure 7. Kaplan-Meier curves of PFS as assessed by BICR at the time of final analysis and Kaplan-Meier curves of OS at the time of interim analysis in the Ami/Laz and Laz groups (Left figure, PFS: Right figure, OS) (FAS, data cutoff date of August 11, 2023)

The results of the final analysis of PFS and the Kaplan-Meier curves in the Japanese subgroup of the MARIPOSA study are shown in Table 39 and Figure 8, respectively.

Table 39. Results of final analysis of PFS in Japanese subgroup (BICR, FAS, data cutoff date of August 11, 2023)

	Ami/Laz	Osi
N	29	32
No. of events (%)	9 (31.0)	16 (50.0)
Median [95% CI] (months)	－ [20.99, －]	18.50 [15.77, －]
Hazard ratio [95% CI]*	0.55 [0.24, 1.25]	

－, Not estimable, *Unstratified Cox proportional-hazards model

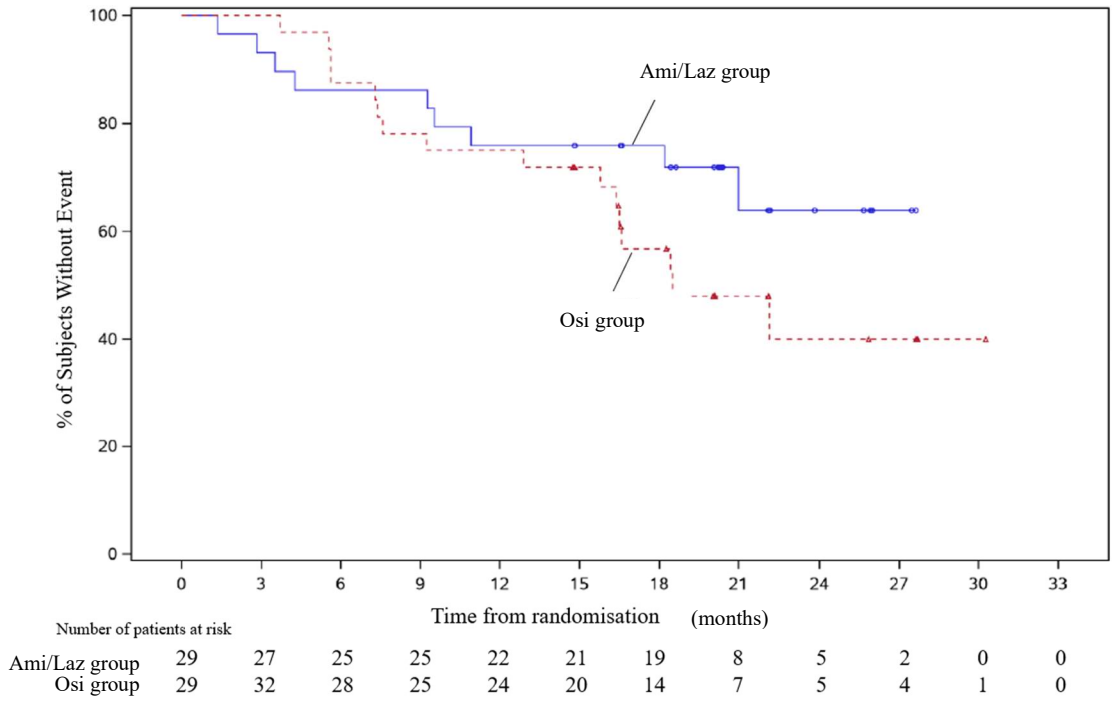

Figure 8. Kaplan-Meier curves of PFS at the time of final analysis in Japanese subgroup (BICR, FAS, data cutoff date of August 11, 2023)

PMDA's view:

For the following reasons etc., the efficacy of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy was demonstrated.

- The MARIPOSA study demonstrated the superiority of Ami/Laz over Osi and a clinically meaningful improvement in the primary endpoint of PFS as assessed by BICR.
- The number of Japanese patients treated with Ami/Laz was limited in the MARIPOSA study, and there are limitations to evaluating the efficacy of Ami/Laz in Japanese patients based on the results from the Japanese subgroup of the MARIPOSA study. However, given that there was no trend towards differences in the results of the primary endpoint of PFS as assessed by BICR between the Japanese subgroup and the overall population, etc., the efficacy of Ami/Laz is expected also in Japanese patients.
- At the time of regulatory review, there was no trend towards shorter OS in the Ami/Laz group than in the Osi group in the MARIPOSA study.

The incidence of deaths within 6 months after randomization was higher in the Ami/Laz group than in the Osi group in the MARIPOSA study, and this information should be provided appropriately to healthcare professionals in clinical practice.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC are shown in the table below.

Although attention should be paid to the possible occurrence of the adverse events listed in the table below during the use of Ami and Laz, Ami/Laz is tolerable as long as physicians with sufficient knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., patient monitoring, management of adverse events, and dose interruption of Ami or Laz.

Ami	In addition to infusion reactions, ILD, skin disorders (including paronychia), venous thromboembolism, fluid retention (including edema and hypoalbuminemia), and diarrhea (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024"), arterial thromboembolism (Ami in combination with Laz)
Laz	ILD, venous thromboembolism, arterial thromboembolism (Laz in combination with Ami), hepatic dysfunction, severe diarrhoea, skin disorders (including paronychia), cardiac failure, and corneal disorders

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of Ami/Laz based on the safety information from the MARIPOSA study:

Safety data from the MARIPOSA study are summarized in Table 40. Table 41 and Table 42 show adverse events reported at a certain level of incidence[67)] in the Ami/Laz group.

[67)] All adverse events with an incidence of ≥10%, Grade ≥3 adverse events with an incidence of ≥5%, adverse events leading to death with an incidence of ≥1%, serious adverse events or adverse events leading to treatment discontinuation with an incidence of ≥2%, adverse events leading to dose or infusion interruption or dose reduction with an incidence of ≥5%, adverse events leading to reduction in infusion rate of Ami with an incidence of ≥10%

Table 40. Summary of safety data (MARIPOSA study, data cutoff date of August 11, 2023)

	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
All adverse events	421 (100)	425 (99.3)	213 (100)
Grade ≥3 adverse events	316 (75.1)	183 (42.8)	97 (45.5)
Adverse events leading to death	34 (8.1)	31 (7.2)	12 (5.6)
Serious adverse events	205 (48.7)	143 (33.4)	75 (35.2)
Adverse events leading to treatment discontinuation*	147 (34.9)	58 (13.6)	28 (13.1)
Ami	145 (34.4)	—	—
Laz	85 (20.2)	—	28 (13.1)
Osi	—	58 (13.6)	—
Adverse events leading to dose or infusion interruption*	382 (90.7)	165 (38.6)	92 (43.2)
Ami	370 (87.9)	—	—
Laz	299 (71.0)	—	92 (43.2)
Osi	—	165 (38.6)	—
Adverse events leading to dose reduction*	249 (59.1)	23 (5.4)	27 (12.7)
Ami	193 (45.8)	—	—
Laz	176 (41.8)	—	27 (12.7)
Osi	—	23 (5.4)	—
Adverse events leading to reduction in infusion rate of Ami	193 (45.8)	—	—

—, Not applicable, * Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 41. Adverse events reported at a certain level of incidence [*1] in the Ami/Laz group (MARIPOSA study, data cutoff date of August 11, 2023)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
All adverse events			
Paronychia	288 (68.4)	121 (28.3)	61 (28.6)
Infusion related reaction	265 (62.9)	0	0
Rash	260 (61.8)	131 (30.6)	95 (44.6)
Hypoalbuminaemia	204 (48.5)	26 (6.1)	17 (8.0)
ALT increased	152 (36.1)	57 (13.3)	50 (23.5)
Oedema peripheral	150 (35.6)	24 (5.6)	24 (11.3)
Constipation	123 (29.2)	55 (12.9)	37 (17.4)
Diarrhoea	123 (29.2)	190 (44.4)	68 (31.9)
Dermatitis acneiform	122 (29.0)	55 (12.9)	45 (21.1)
Stomatitis	122 (29.0)	90 (21.0)	38 (17.8)
AST increased	121 (28.7)	58 (13.6)	45 (21.1)
COVID-19	111 (26.4)	103 (24.1)	42 (19.7)
Decreased appetite	103 (24.5)	76 (17.8)	31 (14.6)
Pruritus	99 (23.5)	73 (17.1)	36 (16.9)
Anaemia	96 (22.8)	91 (21.3)	43 (20.2)
Nausea	90 (21.4)	58 (13.6)	38 (17.8)
Hypocalcaemia	88 (20.9)	35 (8.2)	15 (7.0)
Asthenia	78 (18.5)	46 (10.7)	31 (14.6)
Pulmonary embolism	73 (17.3)	20 (4.7)	15 (7.0)
Fatigue	70 (16.6)	42 (9.8)	23 (10.8)
Muscle spasms	70 (16.6)	32 (7.5)	50 (23.5)
Dry skin	67 (15.9)	60 (14.0)	38 (17.8)
Thrombocytopenia	66 (15.7)	84 (19.6)	20 (9.4)
Cough	65 (15.4)	88 (20.6)	37 (17.4)
Pain in extremity	64 (15.2)	22 (5.1)	21 (9.9)
GGT increased	61 (14.5)	31 (7.2)	20 (9.4)
Deep vein thrombosis	61 (14.5)	11 (2.6)	7 (3.3)
Hypokalaemia	60 (14.3)	30 (7.0)	12 (5.6)
Paraesthesia	58 (13.8)	25 (5.8)	33 (15.5)
Headache	55 (13.1)	54 (12.6)	39 (18.3)
Myalgia	53 (12.6)	19 (4.4)	11 (5.2)
Vomiting	52 (12.4)	23 (5.4)	24 (11.3)
Blood ALP increased	52 (12.4)	22 (5.1)	16 (7.5)
Pyrexia	51 (12.1)	37 (8.6)	20 (9.4)
Dyspnoea	51 (12.1)	68 (15.9)	26 (12.2)
Blood lactate dehydrogenase increased	49 (11.6)	24 (5.6)	21 (9.9)
Dizziness	49 (11.6)	31 (7.2)	14 (6.6)
Back pain	48 (11.4)	45 (10.5)	22 (10.3)
Conjunctivitis	46 (10.9)	7 (1.6)	7 (3.3)
Mucosal inflammation	44 (10.5)	12 (2.8)	8 (3.8)
Grade ≥3 adverse events			
Rash	65 (15.4)	3 (0.7)	4 (1.9)
Paronychia	46 (10.9)	2 (0.5)	2 (0.9)
Dermatitis acneiform	35 (8.3)	0	0
Pulmonary embolism	35 (8.3)	10 (2.3)	8 (3.8)
Infusion related reaction	27 (6.4)	0	0
Hypoalbuminaemia	22 (5.2)	0	0
ALT increased	21 (5.0)	8 (1.9)	6 (2.8)

*1 All adverse events with an incidence of ≥10%, Grade ≥3 adverse events with an incidence of ≥5%

Table 42. Serious adverse events etc. reported at a certain level of incidence[*1] in the Ami/Laz group (MARIPOSA study, data cutoff date of August 11, 2023)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Adverse events leading to death			
Pneumonia	5 (1.2)	4 (0.9)	2 (0.9)
Serious adverse events			
Pulmonary embolism	26 (6.2)	10 (2.3)	8 (3.8)
Pneumonia	17 (4.0)	21 (4.9)	7 (3.3)
Deep vein thrombosis	12 (2.9)	2 (0.5)	1 (0.5)
COVID-19	10 (2.4)	10 (2.3)	3 (1.4)
Pleural effusion	9 (2.1)	17 (4.0)	3 (1.4)
Infusion related reaction	9 (2.1)	0	0
Adverse events leading to treatment discontinuation[*2]			
Infusion related reaction	19 (4.5)	0	0
Paronychia	14 (3.3)	0	1 (0.5)
Rash	11 (2.6)	0	0
Adverse events leading to dose or infusion interruption[*2]			
Infusion related reaction	229 (54.4)	0	0
Rash	104 (24.7)	4 (0.9)	9 (4.2)
Paronychia	91 (21.6)	4 (0.9)	4 (1.9)
COVID-19	63 (15.0)	36 (8.4)	12 (5.6)
Dermatitis acneiform	50 (11.9)	1 (0.2)	3 (1.4)
ALT increased	30 (7.1)	12 (2.8)	7 (3.3)
Hypoalbuminaemia	25 (5.9)	0	0
AST increased	23 (5.5)	11 (2.6)	5 (2.3)
Adverse events leading to dose reduction[*2]			
Rash	84 (20.0)	2 (0.5)	3 (1.4)
Paronychia	80 (19.0)	1 (0.2)	0
Dermatitis acneiform	38 (9.0)	0	0
Adverse events leading to reduction in infusion rate of Ami			
Infusion related reaction	191 (45.4)	0	0

*1 Adverse events leading to death with an incidence of ≥1%, serious adverse events or adverse events leading to treatment discontinuation with an incidence of ≥2%, adverse events leading to dose or infusion interruption or dose reduction with an incidence of ≥5%, adverse events leading to reduction in infusion rate of Ami with an incidence of ≥10%
*2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

PMDA's view:

Since adverse events reported at a certain level of incidence in the Ami/Laz group of the MARIPOSA study may occur following administration of Ami/Laz, the patient's condition should be closely monitored.

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

The applicant's explanation about differences in the safety of Ami/Laz between Japanese and non-Japanese populations, based on the safety information from the MARIPOSA study:

Safety data from Japanese and non-Japanese patients in the Ami/Laz group of the MARIPOSA study are summarized in Table 43. Table 44 shows adverse events reported at a higher incidence in Japanese patients than in non-Japanese patients.[68)]

[68)] All adverse events reported at a ≥20% higher incidence, Grade ≥3 adverse events reported at a ≥10% higher incidence, other adverse events reported at a ≥5% higher incidence

Table 43. Summary of safety data (Ami/Laz group of MARIPOSA study, data cutoff date of August 11, 2023)

	n (%)	
	Japanese patients N = 29	Non-Japanese patients N = 392
All adverse events	29 (100)	392 (100)
Grade ≥3 adverse events	22 (75.9)	294 (75.0)
Adverse events leading to death	1 (3.4)	33 (8.4)
Serious adverse events	13 (44.8)	192 (49.0)
Adverse events leading to treatment discontinuation*	6 (20.7)	141 (36.0)
Ami	6 (20.7)	139 (35.5)
Laz	4 (13.8)	81 (20.7)
Adverse events leading to dose or infusion interruption*	28 (96.6)	354 (90.3)
Ami	26 (89.7)	344 (87.8)
Laz	26 (89.7)	273 (69.6)
Adverse events leading to dose reduction*	19 (65.5)	230 (58.7)
Ami	16 (55.2)	177 (45.2)
Laz	14 (48.3)	162 (41.3)
Adverse events leading to reduction in infusion rate of Ami	9 (31.0)	184 (46.9)

* Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 44. Adverse events reported at a higher incidence*1 in Japanese patients than in non-Japanese patients (Ami/Laz group of MARIPOSA study, data cutoff date of August 11, 2023)

PT (MedDRA ver.25.0)	n (%)	
	Japanese patients N = 29	Non-Japanese patients N = 392
All adverse events		
Paronychia	26 (89.7)	262 (66.8)
Dermatitis acneiform	17 (58.6)	105 (26.8)
Constipation	14 (48.3)	109 (27.8)
Hypoalbuminaemia	20 (69.0)	184 (46.9)
Lymphopenia	7 (24.1)	15 (3.8)
Grade ≥3 adverse events		
Hypoalbuminaemia	5 (17.2)	17 (4.3)
Deep vein thrombosis	4 (13.8)	8 (2.0)
Adverse events leading to treatment discontinuation*2		
Deep vein thrombosis	2 (6.9)	1 (0.3)
Pulmonary embolism	2 (6.9)	6 (1.5)
Adverse events leading to dose or infusion interruption*2		
Dermatitis acneiform	8 (27.6)	42 (10.7)
Deep vein thrombosis	4 (13.8)	15 (3.8)
Hypoalbuminaemia	4 (13.8)	21 (5.4)
Oedema peripheral	3 (10.3)	17 (4.3)
Pulmonary embolism	3 (10.3)	17 (4.3)
Malaise	2 (6.9)	2 (0.5)
Cellulitis	2 (6.9)	5 (1.3)
Anaemia	2 (6.9)	6 (1.5)
Decreased appetite	2 (6.9)	7 (1.8)
Adverse events leading to dose reduction*2		
Dermatitis acneiform	8 (27.6)	30 (7.7)

*1 All adverse events reported at a ≥20% higher incidence, Grade ≥3 adverse events reported at a ≥10% higher incidence, other adverse events reported at a ≥5% higher incidence (There were no adverse events leading to death, serious adverse events, or adverse events leading to reduction in infusion rate of Ami that were reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients)
*2 Adverse events leading to dose or infusion interruption or dose reduction of any study drug

PMDA's view:

Although there are limitations to comparison of safety between Japanese and non-Japanese populations due to the limited number of Japanese patients treated with Ami/Laz in the MARIPOSA study, some adverse events were reported at a higher incidence in Japanese patients than in non-Japanese patients in the MARIPOSA study,

and attention should be paid to the possible occurrence of these events following administration of Ami/Laz. However, given that Ami/Laz is used under the supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy, Ami/Laz is tolerable also in Japanese patients.

The need for a warning/precaution for Laz or Ami/Laz should be determined for some events because a certain number of serious adverse events were reported in the clinical studies of Laz monotherapy including the MARIPOSA study; these events require attention following administration of the existing EGFR-TKIs; or the incidences of these events were clearly high in the Ami/Laz group of the MARIPOSA study, even taking account of those in the clinical studies of Ami or Laz monotherapy. These events are described in the following sections.

7.R.3.3 ILD

The applicant's explanation about ILD[69)] associated with Laz:

The incidence of ILD in the MARIPOSA study is shown in Table 45 and Table 46. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of ILD (min., max.) (days) were 78 (29, 457), 99.5 (9, 512), and 169 (57, 225), respectively.

Table 45. Incidence of ILD (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD*	15 (3.6)	7 (1.7)	16 (3.7)	6 (1.4)	6 (2.8)	3 (1.4)
Pneumonitis	8 (1.9)	4 (1.0)	8 (1.9)	4 (0.9)	3 (1.4)	1 (0.5)
Interstitial lung disease	5 (1.2)	2 (0.5)	5 (1.2)	2 (0.5)	3 (1.4)	2 (0.9)
Hypersensitivity pneumonitis	1 (0.2)	1 (0.2)	0	0	0	0
Lung opacity	1 (0.2)	0	0	0	0	0
Bronchiolitis	0	0	2 (0.5)	0	0	0
Radiation pneumonitis	0	0	1 (0.2)	0	0	0

*Any event of ILD

[69)] Events in the MedDRA SMQ "interstitial lung disease (narrow)" were counted.

Table 46. Incidence of serious ILD etc. (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
ILD leading to death	1 (0.2)	2 (0.5)	0
Pneumonitis	1 (0.2)	0	0
Interstitial lung disease	0	2 (0.5)	0
Serious ILD	13 (3.1)	14 (3.3)	6 (2.8)
Pneumonitis	7 (1.7)	8 (1.9)	3 (1.4)
Interstitial lung disease	5 (1.2)	5 (1.2)	3 (1.4)
Hypersensitivity pneumonitis	1 (0.2)	0	0
Radiation pneumonitis	0	1 (0.2)	0
ILD leading to treatment discontinuation*	13 (3.1)	12 (2.8)	6 (2.8)
Pneumonitis	7 (1.7)	7 (1.6)	3 (1.4)
Interstitial lung disease	5 (1.2)	4 (0.9)	3 (1.4)
Hypersensitivity pneumonitis	1 (0.2)	0	0
Radiation pneumonitis	0	1 (0.2)	0
ILD leading to dose or infusion interruption*	2 (0.5)	3 (0.7)	0
Pneumonitis	1 (0.2)	1 (0.2)	0
Lung opacity	1 (0.2)	0	0
Interstitial lung disease	0	2 (0.5)	0
ILD leading to dose reduction*	0	0	0

* Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 47 shows the details of patients with serious ILD for which a causal relationship to Ami or Laz could not be ruled out[70] in the MARIPOSA study, Study NSC1001, and Study EDI1001.

[70] The following events
- In the MARIPOSA study, Study NSC1003, Study NSC1004, Study NSC1006, Study NSC1007, Study NSC1008, and Study NSC1009, the events assessed by the investigator as (1) related to Ami or Laz on the causality scale [(1) related or (2) not related]
- In Study NSC1001 and Study EDI1001, the events assessed by the investigator as (1) very likely related, (2) probably related, or (3) possibly related to Ami or Laz on the causality scale [(1) very likely, (2) probable, (3) possible, (4) doubtful, or (5) not related]
- In Study 101, Study NSC2001, and Study 301, the events assessed by the investigator as (1) certainly related, (2) probably/likely related, or (3) possibly related to Ami or Laz, or (4) unassessable/unclassifiable on the causality scale [(1) certain, (2) probable/likely, (3) possible, (4) unassessable/unclassifiable, (5) unlikely, or (6) not related]

Table 47. Listing of patients with serious ILD for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	Race	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Laz group)	7[redacted]	F	Japanese	Pneumonitis	1	225	43	—	Discontinued	Resolved	Laz
	6[redacted]	F	Non-Japanese	Pneumonitis	3	216	36	—	Discontinued	Resolving	Laz
	6[redacted]	F	Non-Japanese	Interstitial lung disease	1	221	279	—	Discontinued	Resolved	Laz
	6[redacted]	F	Non-Japanese	Interstitial lung disease	3	97	29	—	Discontinued	Resolving	Laz
				Interstitial lung disease	2	125	23	—	Not applicable	Resolving	Laz
	5[redacted]	F	Non-Japanese	Interstitial lung disease	3	169	22	—	Discontinued	Resolved	Laz
MARIPOSA (Ami/Laz group)	6[redacted]	F	Non-Japanese	Pneumonitis	2	283	27	Discontinued	Discontinued	Resolved	Laz
	7[redacted]	M	Japanese	Pneumonitis	1	43	7	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
				Pneumonitis	3	50	11	Discontinued	Discontinued	Resolving	Ami and Laz
				Pneumonitis	2	61	95	Not applicable	Not applicable	Resolved	Ami and Laz
	5[redacted]	F	Non-Japanese	Interstitial lung disease	2	166	19	Discontinued	Discontinued	Resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Interstitial lung disease	2	110	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz
	7[redacted]	M	Non-Japanese	Pneumonitis	4	78	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz
	6[redacted]	M	Non-Japanese	Interstitial lung disease	1	56	8	Discontinued	Discontinued	Not resolved	Ami and Laz
				Interstitial lung disease	2	63	13	Not applicable	Not applicable	Not resolved	Ami and Laz
				Interstitial lung disease	3	75	27	Not applicable	Not applicable	Resolving	Ami and Laz
	6[redacted]	M	Non-Japanese	Interstitial lung disease	2	29	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Pneumonitis	2	114	191	Discontinued	Discontinued	Resolving	Ami and Laz
	7[redacted]	F	Non-Japanese	Pneumonitis	3	82	17	Discontinued	Discontinued	Not resolved	Ami and Laz
				Pneumonitis	5	99	1	Not applicable	Not applicable	Fatal	Ami and Laz
	7[redacted]	F	Non-Japanese	Pneumonitis	3	39	31	Discontinued	Discontinued	Not resolved	Ami and Laz
	7[redacted]	F	Non-Japanese	Interstitial lung disease	3	443	14	Discontinued	Discontinued	Resolving	Ami and Laz
	4[redacted]	M	Non-Japanese	Pneumonitis	1	280	Unknown	Discontinued	Discontinued	Not resolved	Ami
	6[redacted]	F	Non-Japanese	Hypersensitivity pneumonitis	4	39	14	Discontinued	Discontinued	Resolving	Ami
				Hypersensitivity pneumonitis	2	52	5	Not applicable	Not applicable	Not resolved	Ami
				Hypersensitivity pneumonitis	4	56	28	Not applicable	Not applicable	Not resolved	Ami

NSC1001 (Ami/Laz*)	6[redacted]	F	Japanese	Pneumonitis	3	254	23	Not applicable	Not applicable	Resolving	Laz
	5[redacted]	M	Japanese	Pneumonitis	3	84	6	Discontinued	Discontinued	Resolving	Ami and Laz
	6[redacted]	F	Non-Japanese	Pneumonitis	3	34	10	Discontinued	Discontinued	Not resolved	Ami and Laz
				Pneumonitis	4	43	Unknown	Not applicable	Not applicable	Not resolved	Ami and Laz
	6[redacted]	M	Non-Japanese	Pneumonitis	2	115	10	None	None	Not resolved	Ami and Laz
	7[redacted]	F	Non-Japanese	Interstitial lung disease	4	115	14	Discontinued	Discontinued	Resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Interstitial lung disease	4	43	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz
	5[redacted]	F	Non-Japanese	Pneumonitis	4	43	12	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
				Pneumonitis	5	55	1	Discontinued	Discontinued	Fatal	Ami and Laz
	6[redacted]	F	Non-Japanese	Pneumonitis	2	124	47	Discontinued	Discontinued	Not resolved	Ami and Laz
	5[redacted]	F	Non-Japanese	Pneumonitis	3	59	27	Discontinued	Discontinued	Not resolved	Ami and Laz
				Pneumonitis	4	86	Unknown	Not applicable	Not applicable	Not resolved	Ami and Laz
	4[redacted]	F	Non-Japanese	Pneumonitis	1	54	Unknown	Discontinued	Discontinued	Resolved	Ami and Laz
	4[redacted]	M	Non-Japanese	Pneumonitis	4	14	Unknown	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
	7[redacted]	M	Non-Japanese	Pneumonitis	2	40	26	Discontinued	Discontinued	Resolved	Ami and Laz
EDI1001 (Ami/Laz cohort)	4[redacted]	M	Non-Japanese	Pneumonitis	3	25	9	Discontinued	Discontinued	Not resolved	Ami and Laz
				Pneumonitis	5	34	1	Not applicable	Not applicable	Fatal	Ami and Laz
	5[redacted]	M	Non-Japanese	Interstitial lung disease	3	81	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

PMDA's view:

Given that multiple cases of serious ILD whose causal relationship to Laz could be rationally explained were reported in the clinical studies of Laz monotherapy including the MARIPOSA study, and that ILD is a known risk associated with the existing EGFR-TKIs, attention should be paid to the possible occurrence of ILD following administration of Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of ILD in the clinical studies of Laz monotherapy, using the Laz package insert and other materials.

7.R.3.4 Venous thromboembolism

The applicant's explanation about venous thromboembolism[71)] associated with Laz or Ami/Laz:

The incidence of venous thromboembolism in the MARIPOSA study is shown in Table 48 and Table 49. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of venous thromboembolism (min., max.) (days) were 84 (6, 777), 194 (10, 675), and 250 (32, 774), respectively. During the first approximately 4 months of study treatment, the incidence of venous thromboembolism tended to be higher in the Ami/Laz group than in the Osi and Laz groups [see Figure 9].

[71)] Events in the MedDRA SMQ "embolic and thrombotic events, venous (narrow)" and events coded to the MedDRA PTs "thrombosis" and "embolism" were counted.

Table 48. Incidence of venous thromboembolism[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism[*2]	157 (37.3)	47 (11.2)	39 (9.1)	15 (3.5)	30 (14.1)	12 (5.6)
Pulmonary embolism	73 (17.3)	35 (8.3)	20 (4.7)	10 (2.3)	15 (7.0)	8 (3.8)
Deep vein thrombosis	61 (14.5)	12 (2.9)	11 (2.6)	2 (0.5)	7 (3.3)	2 (0.9)
Venous thrombosis limb	17 (4.0)	2 (0.5)	1 (0.2)	0	4 (1.9)	3 (1.4)
Thrombosis	9 (2.1)	0	1 (0.2)	0	2 (0.9)	0
Venous thrombosis	8 (1.9)	2 (0.5)	1 (0.2)	0	0	0
Superficial vein thrombosis	6 (1.4)	0	0	0	2 (0.9)	0
Thrombophlebitis	6 (1.4)	0	4 (0.9)	0	0	0
Embolism	4 (1.0)	0	3 (0.7)	3 (0.7)	0	0
Embolism venous	4 (1.0)	1 (0.2)	1 (0.2)	0	2 (0.9)	0
Jugular vein thrombosis	3 (0.7)	0	0	0	0	0
Pulmonary infarction	2 (0.5)	0	0	0	0	0

*1 Incidence by PT is presented for adverse events reported by ≥2 subjects in any group. *2 Any event of venous thromboembolism

Table 49. Incidence of serious venous thromboembolism etc. (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Venous thromboembolism leading to death	2 (0.5)	2 (0.5)	2 (0.9)
Pulmonary embolism	2 (0.5)	2 (0.5)	2 (0.9)
Serious venous thromboembolism	46 (10.9)	15 (3.5)	11 (5.2)
Pulmonary embolism	26 (6.2)	10 (2.3)	8 (3.8)
Deep vein thrombosis	12 (2.9)	2 (0.5)	1 (0.5)
Venous thrombosis	4 (1.0)	0	0
Venous thrombosis limb	4 (1.0)	0	3 (1.4)
Jugular vein thrombosis	2 (0.5)	0	0
Embolism venous	1 (0.2)	0	0
Superior sagittal sinus thrombosis	1 (0.2)	0	0
Thrombosis	1 (0.2)	0	0
Embolism	0	2 (0.5)	0
Superior vena cava syndrome	0	1 (0.2)	0
Venous thromboembolism leading to treatment discontinuation[*]	12 (2.9)	2 (0.5)	3 (1.4)
Pulmonary embolism	8 (1.9)	2 (0.5)	3 (1.4)
Deep vein thrombosis	3 (0.7)	0	0
Superior sagittal sinus thrombosis	1 (0.2)	0	0
Vena cava thrombosis	1 (0.2)	0	0
Venous thrombosis limb	1 (0.2)	0	0
Venous thromboembolism leading to dose or infusion interruption[*]	47 (11.2)	10 (2.3)	5 (2.3)
Pulmonary embolism	20 (4.8)	9 (2.1)	3 (1.4)
Deep vein thrombosis	19 (4.5)	2 (0.5)	1 (0.5)
Venous thrombosis limb	7 (1.7)	1 (0.2)	2 (0.9)
Embolism	2 (0.5)	0	0
Jugular vein thrombosis	2 (0.5)	0	0
Venous thrombosis	2 (0.5)	0	0
Axillary vein thrombosis	1 (0.2)	0	0
Embolism venous	1 (0.2)	0	0
Portal vein thrombosis	1 (0.2)	0	0
Superior sagittal sinus thrombosis	1 (0.2)	0	0
Thrombophlebitis	1 (0.2)	0	0
Thrombosis	1 (0.2)	0	0
Venous thromboembolism leading to dose reduction[*]	5 (1.2)	0	2 (0.9)
Deep vein thrombosis	2 (0.5)	0	0
Pulmonary embolism	2 (0.5)	0	1 (0.5)
Venous thrombosis limb	1 (0.2)	0	1 (0.5)

*Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

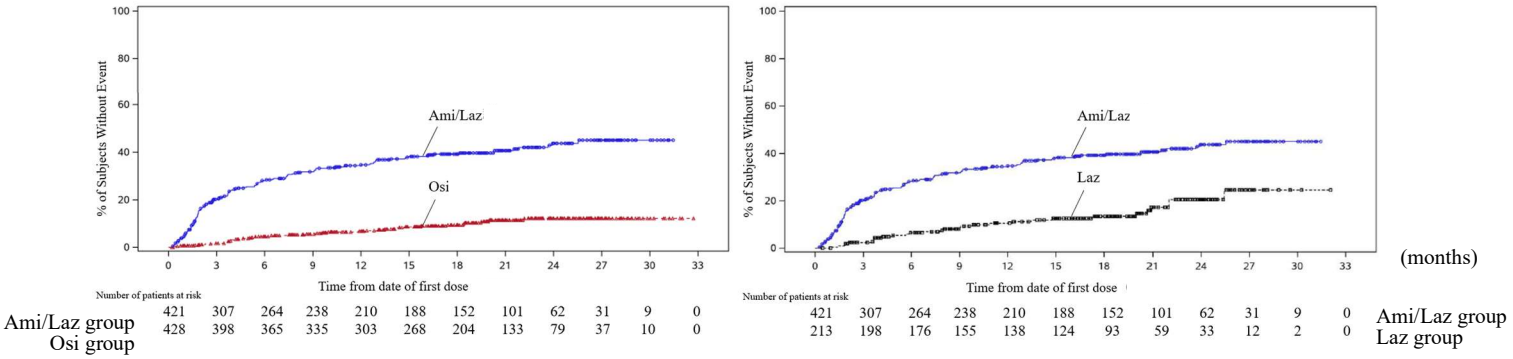

Figure 9. Kaplan-Meier curves for the time to the first onset of venous thromboembolism (MARIPOSA study)
(Left figure, Ami/Laz group vs. Osi group; Right figure, Ami/Laz group vs. Laz group)
(Safety analysis set, data cutoff date of August 11, 2023)

Table 50 shows the details of patients with serious venous thromboembolism for which a causal relationship to Ami or Laz could not be ruled out[70)] in the MARIPOSA study, Study NSC1001, and Study EDI1001.

Table 50. Listing of patients with serious venous thromboembolism for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	Race	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Prior/ current thrombosis	Anticoagulant use at onset	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Laz group)	7[redacted]	F	Non-Japanese	Pulmonary embolism	3	111	15	No	No	—	Dose interrupted	Resolving	Laz
	6[redacted]	F	Non-Japanese	Pulmonary embolism	3	112	14	No	No	—	Dose interrupted	Resolving	Laz
				Venous thrombosis limb	3	721	Unknown	No	No	—	Dose interrupted	Resolved	Laz
	6[redacted]	F	Non-Japanese	Venous thrombosis limb	3	57	9	No	No	—	Dose interrupted	Resolving	Laz
				Venous thrombosis limb	2	65	Unknown	No	Yes	—	Dose reduced	Not resolved	Laz
	6[redacted]	M	Non-Japanese	Venous thrombosis limb	3	774	Unknown	No	No	—	None	Not resolved	Laz
	7[redacted]	F	Non-Japanese	Deep vein thrombosis	3	609	Unknown	No	No	—	None	Not resolved	Laz

MARIPOSA (Ami/Laz group)	6[redacted]	M	Non-Japanese	Superior sagittal sinus thrombosis	2	278	10	No	No	Dose interrupted	Dose interrupted	Resolving	Laz
	6[redacted]	F	Non-Japanese	Pulmonary embolism	3	353	9	No	No	None	None	Resolving	Laz
	6[redacted]	M	Japanese	Pulmonary embolism	3	112	19	No	No	Discontinued	Discontinued	Resolving	Ami and Laz
	5[redacted]	F	Japanese	Deep vein thrombosis	3	61	9	No	No	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
				Deep vein thrombosis	2	70	Unknown			None	None	Not resolved	Ami and Laz
	7[redacted]	M	Japanese	Pulmonary embolism	3	96	11	Yes	No	Discontinued	Dose interrupted	Resolved	Ami and Laz
	8[redacted]	F	Non-Japanese	Pulmonary embolism	3	175	8	No	No	Dose interrupted	Dose interrupted	Sequelae	Ami and Laz
	6[redacted]	M	Non-Japanese	Pulmonary embolism	3	43	7	No	No	None	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	F	Non-Japanese	Embolism venous	3	43	5	No	No	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	5[redacted]	M	Non-Japanese	Pulmonary embolism	2	450	6	No	No	None	None	Resolved	Ami and Laz
	6[redacted]	M	Non-Japanese	Pulmonary embolism	3	335	17	No	No	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	M	Non-Japanese	Venous thrombosis limb	3	260	28	No	Yes	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
				Venous thrombosis limb	2	287	51			Dose interrupted	None	Resolving	Ami
				Venous thrombosis limb	1	337	Unknown			None	None	Not resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Pulmonary embolism	3	301	Unknown	No	Yes	None	Dose interrupted	Not resolved	Ami and Laz
	5[redacted]	F	Non-Japanese	Pulmonary embolism	3	54	11	Yes	No	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	5[redacted]	F	Non-Japanese	Pulmonary embolism	3	112	22	No	No	Dose interrupted	None	Resolved	Ami and Laz
				Venous thrombosis limb	2	134	Unknown		Yes	Dose interrupted	None	Not resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Deep vein thrombosis	2	44	29	No	No	Dose interrupted	None	Resolved	Ami and Laz
				Venous thrombosis limb	2	674	4	No	No	None	None	Resolving	Ami and Laz
	6[redacted]	F	Non-Japanese	Pulmonary embolism	3	95	9	No	No	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
				Venous thrombosis	2	128	7			None	None	Resolving	Ami and Laz
	8[redacted]	F	Non-Japanese	Pulmonary embolism	3	283	13	No	No	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	F	Non-Japanese	Deep vein thrombosis	3	320	6	No	No	Dose interrupted	None	Resolved	Ami and Laz
	5[redacted]	F	Non-Japanese	Jugular vein thrombosis	2	148	2	No	Yes	None	None	Resolved	Ami and Laz
	6[redacted]	F	Non-Japanese	Pulmonary embolism	3	12	Unknown	No	No	None	None	Not resolved	Ami
	6[redacted]	M	Non-Japanese	Pulmonary embolism	2	70	45	No	No	None	None	Resolved	Ami
	5[redacted]	F	Non-Japanese	Venous thrombosis limb	2	75	Unknown	No	No	None	None	Not resolved	Ami
	7[redacted]	M	Non-Japanese	Pulmonary embolism	3	51	90	No	Yes	Dose interrupted	Dose interrupted	Resolved	Ami
	3[redacted]	F	Non-Japanese	Venous thrombosis	3	631	5	No	No	None	None	Resolved	Ami
	7[redacted]	F	Non-Japanese	Deep vein thrombosis	2	30	3	No	No	Dose interrupted	None	Not resolved	Ami
				Deep vein thrombosis	3	33	10			Dose interrupted	Dose interrupted	Resolving	Ami
	6[redacted]	F	Non-Japanese	Pulmonary embolism	4	217	10	Yes	No	Dose interrupted	Dose interrupted	Resolving	Ami
	4[redacted]	F	Non-Japanese	Pulmonary embolism	3	332	5	No	No	Dose interrupted	None	Resolving	Ami

NSC1001 (Ami/Laz*)	7[redacted]	F	Non-Japanese	Pulmonary embolism	3	22	3	No	Unknown	None	Dose reduced	Resolving	Laz
	7[redacted]	M	Non-Japanese	Pulmonary embolism	3	50	Unknown	No	Unknown	None	Dose interrupted	Not resolved	Laz
	6[redacted]	M	Japanese	Deep vein thrombosis	2	215	53	Yes	Unknown	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	6[redacted]	M	Non-Japanese	Pulmonary embolism	3	25	5	No	Unknown	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
				Pulmonary embolism	2	29	Unknown	No	Unknown	None	None	Not resolved	Ami and Laz
	6[redacted]	M	Non-Japanese	Pulmonary embolism	3	42	9	No	Unknown	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	5[redacted]	M	Non-Japanese	Embolism	3	58	7	Yes	Unknown	None	None	Resolving	Ami and Laz
	8[redacted]	F	Non-Japanese	Pulmonary embolism	3	96	20	No	Unknown	None	None	Not resolved	Ami and Laz
	7[redacted]	M	Non-Japanese	Pulmonary embolism	2	56	Unknown	No	Unknown	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
EDI1001 (Ami/Laz cohort)	6[redacted]	M	Non-Japanese	Pulmonary embolism	3	483	16	No	Unknown	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	5[redacted]	M	Non-Japanese	Pulmonary embolism	3	209	14	No	Unknown	Discontinued	Discontinued	Resolving	Ami and Laz

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

An independent data monitoring committee (IDMC) pointed out that the incidence of venous thromboembolism was higher in the Ami/Laz group than in the Osi and Laz groups in the MARIPOSA study, and the majority of the events of venous thromboembolism in the Ami/Laz group occurred within 4 months after the start of treatment with Ami/Laz. Given these points, the protocol amendment 3 (as of August 22, 2022) advised administration of prophylactic anticoagulation for the first 4 months of treatment with Ami/Laz. Vitamin K antagonists such as warfarin were not recommended because of numerous drug interactions.

At the time of recommending the above prophylactic anticoagulation, patient enrollment in the MARIPOSA study was complete, and 12 patients were in their first 4 months of treatment with Ami/Laz. A total of 21 patients including these 12 patients received prophylactic anticoagulation at the time of initiation of treatment with Ami/Laz in the MARIPOSA study, and the anticoagulants used were rivaroxaban (7 patients), apixaban (5 patients), enoxaparin sodium (6 patients), and edoxaban; warfarin; and fondaparinux sodium (1 patient each).

PMDA's view:

Given the following points, attention should be paid to the possible occurrence of venous thromboembolism following administration of Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of venous thromboembolism in the clinical studies of Laz monotherapy, using the Laz package insert and other materials. Taking into account that the causal relationship between Laz and venous thromboembolism is unclear at present, the applicant should collect post-marketing information. If any new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

- In the Laz group of the MARIPOSA study, Garde ≥3 venous thromboembolism was reported at a certain level of incidence.

- In the clinical studies of Ami/Laz including the MARIPOSA study, a certain number of cases of serious venous thromboembolism for which a causal relationship to Laz could not be ruled out have been accrued.
- Venous thromboembolism has been reported also with the existing EGFR-TKIs.

Although the package insert and other materials had a precautionary statement about venous thromboembolism associated with Ami at the time of the initial approval of Ami, given the following points, particular attention should be paid to the possible occurrence of venous thromboembolism following administration of Ami/Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of venous thromboembolism in the clinical studies of Ami/Laz, using the package inserts and other materials for Ami and Laz. The use of prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz is described in Section "7.R.5.2 Use of prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz."

- The incidence of venous thromboembolism was higher in the Ami/Laz group of the MARIPOSA study compared with the clinical studies of Laz monotherapy including the MARIPOSA study and the clinical studies that were previously evaluated for the initial approval of Ami (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024").
- In the clinical studies of Ami/Laz including the MARIPOSA study, a certain number of cases of serious venous thromboembolism whose causal relationship to Ami or Laz could be rationally explained have been accrued.

7.R.3.5 Arterial thromboembolism

The applicant's explanation about arterial thromboembolism[72)] associated with Laz or Ami/Laz:
The incidence of arterial thromboembolism in the MARIPOSA study is shown in Table 51 and Table 52. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of arterial thromboembolism (min., max.) (days) were 282.5 (29, 709), 289 (128, 890), and 147, respectively.

[72)] Events in the MedDRA SMQ "embolic and thrombotic events, arterial (narrow)" were counted.

Table 51. Incidence of arterial thromboembolism (MARIPOSA study)

PT (MedDRAver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Arterial thromboembolism*	17 (4.0)	6 (1.4)	6 (1.4)	4 (0.9)	1 (0.5)	0
Myocardial infarction	4 (1.0)	4 (1.0)	1 (0.2)	1 (0.2)	0	0
Peripheral arterial occlusive disease	3 (0.7)	0	1 (0.2)	1 (0.2)	0	0
Ischaemic stroke	2 (0.5)	0	0	0	1 (0.5)	0
Lacunar infarction	2 (0.5)	0	0	0	0	0
Pulmonary artery thrombosis	2 (0.5)	0	0	0	0	0
Acute coronary syndrome	1 (0.2)	1 (0.2)	0	0	0	0
Ischaemic cerebral infarction	1 (0.2)	1 (0.2)	0	0	0	0
Basal ganglia infarction	1 (0.2)		0	0	0	0
Peripheral artery thrombosis	1 (0.2)		0	0	0	0
Transient ischaemic attack	1 (0.2)	0	0	0	0	0
Acute myocardial infarction	0	0	2 (0.5)	2 (0.5)	0	0
Amaurosis fugax	0	0	1 (0.2)	0	0	0
Aortic thrombosis	0	0	1 (0.2)	0	0	0

*Any event of arterial thromboembolism

Table 52. Incidence of serious arterial thromboembolism etc. (MARIPOSA study)

PT (MedDRAver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Arterial thromboembolism leading to death	4 (1.0)	0	0
Myocardial infarction	3 (0.7)	0	0
Ischaemic cerebral infarction	1 (0.2)	0	0
Serious arterial thromboembolism	7 (1.7)	3 (0.7)	0
Myocardial infarction	4 (1.0)	0	0
Acute coronary syndrome	1 (0.2)	0	0
Ischaemic cerebral infarction	1 (0.2)	0	0
Peripheral artery thrombosis	1 (0.2)	0	0
Acute myocardial infarction	0	2 (0.5)	0
Peripheral arterial occlusive disease	0	1 (0.2)	0
Arterial thromboembolism leading to treatment discontinuation*	5 (1.2)	0	0
Myocardial infarction	3 (0.7)	0	0
Ischaemic cerebral infarction	1 (0.2)	0	0
Ischaemic stroke	1 (0.2)	0	0
Arterial thromboembolism leading to dose or infusion interruption*	3 (0.7)	2 (0.5)	0
Acute coronary syndrome	1 (0.2)	0	0
Peripheral artery thrombosis	1 (0.2)	0	0
Pulmonary artery thrombosis	1 (0.2)	0	0
Acute myocardial infarction	0	1 (0.2)	0
Amaurosis fugax	0	1 (0.2)	0
Arterial thromboembolism leading to dose reduction*	0	0	0

*Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 53 shows the details of patients with serious arterial thromboembolism for which a causal relationship to Ami or Laz could not be ruled out[70)] in the clinical studies of Ami/Laz or Laz monotherapy[73)] including the MARIPOSA study.

[73)] Clinical studies of Ami/Laz:
The Ami/Laz group of the MARIPOSA study, Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part of Study NSC1001, Study EDI1001, Study NSC1003, and the PALOMA-3 study
Clinical studies of Laz monotherapy:
The Laz group of the MARIPOSA study, Japanese phase I part of Study NSC1001, Study 101, Study NSC1002, Study NSC1003, Study NSC1004, Study NSC1006, Study NSC1007, Study 1008, Study NSC1009, Study NSC2001, and the Laz group of Study 301

Table 53. Listing of patients with serious arterial thromboembolism for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	Race	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
NSC2001 (Laz monotherapy)	6[redacted]	F	Non-Japanese	Myocardial infarction	3	209	6	—	Dose interrupted	Resolving	Laz
MARIPOSA (Ami/Laz group)	6[redacted]	F	Non-Japanese	Myocardial infarction	3	285	5	None	Discontinued	Not resolved	Ami and Laz
				Myocardial infarction	5	289	1	Discontinued	None	Fatal	Ami and Laz
	8[redacted]	F	Non-Japanese	Myocardial infarction	5	524	1	Discontinued	Discontinued	Fatal	Ami and Laz
NSC1001 (Ami/Laz*)	8[redacted]	F	Japanese	Myocardial infarction	3	6	10	Discontinued	Discontinued	Resolving	Ami and Laz
	7[redacted]	M	Japanese	Peripheral embolism	3	492	8	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
PALOMA-3 (Ami/Laz)	8[redacted]	M	Non-Japanese	Ischaemic stroke	3	299	7	Discontinued	Dose interrupted	Resolved	Ami and Laz
	3[redacted]	F	Non-Japanese	Embolism arterial	2	41	Unknown	None	None	Not resolved	Ami and Laz

PMDA's view:

Given that only 1 case of serious arterial thromboembolism for which a causal relationship to Laz could not be ruled out was reported in the clinical studies of Laz monotherapy including the MARIPOSA study, no particular precautionary statement regarding arterial thromboembolism associated with Laz is needed at present.

On the other hand, given the following points, attention should be paid to the possible occurrence of arterial thromboembolism following administration of Ami/Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of arterial thromboembolism in the clinical studies of Ami/Laz, using the package inserts and other materials for Ami and Laz. Taking into account that the causal relationship between Ami/Laz and arterial thromboembolism is unclear at present, the applicant should collect post-marketing information. If any new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

- In the Ami/Laz group of the MARIPOSA study, Garde ≥3 arterial thromboembolism was reported at a certain level of incidence.
- Arterial thromboembolism has been reported also with the existing drugs targeting EGFR.

7.R.3.6 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with Laz or Ami/Laz[74]:

The incidence of hepatic dysfunction in the MARIPOSA study is shown in Table 54 and Table 55. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of hepatic dysfunction (min., max.) (days) were 196 (1, 925), 223 (1, 843), and 121 (1, 758), respectively.

[74] Events in the MedDRA Sub-SMQs "cholestasis and jaundice of hepatic origin (broad)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "hepatitis, non-infectious," and "liver related investigations, signs and symptoms" were counted.

Table 54. Incidence of hepatic dysfunction*1 (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction*2	289 (68.6)	57 (13.5)	113 (26.4)	19 (4.4)	81 (38.0)	9 (4.2)
Hypoalbuminaemia	204 (48.5)	22 (5.2)	26 (6.1)	0	17 (8.0)	0
ALT increased	152 (36.1)	21 (5.0)	57 (13.3)	8 (1.9)	50 (23.5)	6 (2.8)
AST increased	121 (28.7)	14 (3.3)	58 (13.6)	5 (1.2)	45 (21.1)	3 (1.4)
GGT increased	61 (14.5)	12 (2.9)	31 (7.2)	6 (1.4)	20 (9.4)	2 (0.9)
Blood ALP increased	52 (12.4)	5 (1.2)	22 (5.1)	2 (0.5)	16 (7.5)	1 (0.5)
Hyperbilirubinaemia	28 (6.7)	1 (0.2)	14 (3.3)	0	18 (8.5)	1 (0.5)
Hepatic steatosis	5 (1.2)	0	0	0	0	0
Hepatic function abnormal	4 (1.0)	1 (0.2)	5 (1.2)	2 (0.5)	3 (1.4)	0
Cholestasis	3 (0.7)	0	0	0	0	0
Hepatitis	3 (0.7)	0	0	0	0	0
Ascites	2 (0.5)	0	1 (0.2)	0	0	0
Hepatic cytolysis	2 (0.5)	0	1 (0.2)	0	0	0
Hepatotoxicity	2 (0.5)	0	2 (0.5)	0	0	0
Hypertransaminasaemia	2 (0.5)	0	2 (0.5)	1 (0.2)	0	0
Blood bilirubin increased	1 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.9)	0

*1 Incidence by PT is presented for adverse events reported by ≥2 subjects in any group. *2 Any event of hepatic dysfunction

Table 55. Incidence of serious hepatic dysfunction etc. (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Hepatic dysfunction leading to death	0	0	0
Serious hepatic dysfunction	14 (3.3)	9 (2.1)	5 (2.3)
ALT increased	8 (1.9)	6 (1.4)	4 (1.9)
Hypoalbuminaemia	5 (1.2)	0	0
AST increased	1 (0.2)	4 (0.9)	4 (1.9)
Hepatic function abnormal	1 (0.2)	1 (0.2)	0
Hyperbilirubinaemia	0	1 (0.2)	1 (0.5)
GGT increased	0	1 (0.2)	1 (0.5)
Hepatic dysfunction leading to treatment discontinuation*	9 (2.1)	0	0
Hypoalbuminaemia	6 (1.4)	0	0
ALT increased	3 (0.7)	0	0
AST increased	1 (0.2)	0	0
GGT increased	1 (0.2)	0	0
Hepatotoxicity	1 (0.2)	0	0
Hepatic dysfunction leading to dose or infusion interruption*	60 (14.3)	16 (3.7)	8 (3.8)
ALT increased	30 (7.1)	12 (2.8)	7 (3.3)
Hypoalbuminaemia	25 (5.9)	0	0
AST increased	23 (5.5)	11 (2.6)	5 (2.3)
GGT increased	13 (3.1)	5 (1.2)	2 (0.9)
Blood ALP increased	3 (0.7)	1 (0.2)	1 (0.5)
Hepatic function abnormal	2 (0.5)	1 (0.2)	0
Hyperbilirubinaemia	2 (0.5)	2 (0.5)	1 (0.5)
Blood bilirubin increased	1 (0.2)	1 (0.2)	0
Blood cholinesterase decreased	1 (0.2)	0	0
Hepatitis	1 (0.2)	0	0
Hepatotoxicity	1 (0.2)	0	0
Hypertransaminasaemia	0	1 (0.2)	0
Hepatic dysfunction leading to dose reduction*	21 (5.0)	0	2 (0.9)
Hypoalbuminaemia	11 (2.6)	0	1 (0.5)
ALT increased	8 (1.9)	0	1 (0.5)
AST increased	5 (1.2)	0	1 (0.5)
GGT increased	2 (0.5)	0	1 (0.5)

*Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 56 shows the details of patients with serious hepatic dysfunction for which a causal relationship to Ami or Laz could not be ruled out [70)] in the MARIPOSA study, Study NSC1001, and Study EDI1001.

Table 56. Listing of patients with serious hepatic dysfunction for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Laz group)	4[redacted]	F	ALT increased	1	29	29	—	None	Resolved	Laz
			AST increased	1	29	29	—	None	Resolved	Laz
	6[redacted]	M	GGT increased	3	282	8	—	Dose interrupted	Resolved	Laz
			Hyperbilirubinaemia	3	282	8	—	Dose interrupted	Resolved	Laz
			ALT increased	4	282	12	—	Dose interrupted	Resolved	Laz
			AST increased	4	282	12	—	Dose interrupted	Resolved	Laz
	5[redacted]	F	AST increased	3	57	3	—	Dose interrupted	Resolved	Laz
	5[redacted]	F	AST increased	2	29	1	—	Dose interrupted	Resolving	Laz
			ALT increased	3	29	4	—	Dose interrupted	Resolving	Laz
	6[redacted]	F	ALT increased	3	29	5	—	Dose interrupted	Resolved	Laz
MARIPOSA (Ami/Laz group)	6[redacted]	F	ALT increased	3	463	8	Dose interrupted	Dose interrupted	Resolving	Laz
	4[redacted]	M	AST increased	4	239	1	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	5[redacted]	M	Hypoalbuminaemia	2	83	85	None	None	Resolving	Ami
			ALT increased	3	126	4	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	5[redacted]	F	Hypoalbuminaemia	2	42	7	None	None	Resolving	Ami and Laz
	5[redacted]	M	ALT increased	3	225	8	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	3[redacted]	F	ALT increased	2	8	7	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	7[redacted]	F	ALT increased	2	99	8	None	None	Resolving	Ami and Laz
	6[redacted]	M	Hypoalbuminaemia	2	28	21	Dose interrupted	Dose interrupted	Resolving	Ami
	7[redacted]	M	Hypoalbuminaemia	2	42	19	None	None	Resolving	Ami
			Hypoalbuminaemia	1	60	25	None	None	Not resolved	Ami
			Hypoalbuminaemia	2	84	57	Dose interrupted	None	Resolving	Ami
			Hypoalbuminaemia	1	140	134	Dose reduced	None	Resolved	Ami
	4[redacted]	M	ALT increased	2	8	1	Dose interrupted	Dose interrupted	Resolving	Ami
NSC1001 (Ami/Laz*)	5[redacted]	M	Hypoalbuminaemia	3	60	37	Not applicable	Not applicable	Resolved	Ami and Laz

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

One subject each in the Ami/Laz and Laz groups of the MARIPOSA study met Hy's law laboratory criteria for drug-induced liver injury (defined based on Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) among the clinical studies of Ami/Laz or Laz monotherapy including the MARIPOSA study.[73)] The event in the Ami/Laz group was potentially associated with concomitant medications. In both cases, treatment could be continued after interruption of study drug.

PMDA's view:

Given that multiple cases of serious hepatic dysfunction whose causal relationship to Laz could be rationally explained were reported in the clinical studies of Laz monotherapy including the MARIPOSA study, and that

hepatic dysfunction is a known risk associated with the existing EGFR-TKIs, attention should be paid to the possible occurrence of hepatic dysfunction following administration of Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of hepatic dysfunction in the clinical studies of Laz monotherapy, using the Laz package insert and other materials.

7.R.3.7 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders[75)] associated with Laz or Ami/Laz:

The incidence of gastrointestinal disorders in the MARIPOSA study is shown in Table 57 and Table 58. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of gastrointestinal disorder (min., max.) (days) were 88 (1, 926), 141.5 (1, 876), and 83 (1, 829), respectively.

Table 57. Incidence of gastrointestinal disorders[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders[*2]	326 (77.4)	35 (8.3)	298 (69.6)	14 (3.3)	142 (66.7)	8 (3.8)
Constipation	123 (29.2)	0	55 (12.9)	0	37 (17.4)	1 (0.5)
Diarrhoea	123 (29.2)	9 (2.1)	190 (44.4)	3 (0.7)	68 (31.9)	4 (1.9)
Stomatitis	122 (29.0)	5 (1.2)	90 (21.0)	1 (0.2)	38 (17.8)	1 (0.5)
Nausea	90 (21.4)	5 (1.2)	58 (13.6)	1 (0.2)	38 (17.8)	1 (0.5)
Vomiting	52 (12.4)	2 (0.5)	23 (5.4)	0	24 (11.3)	1 (0.5)
Haemorrhoids	41 (9.7)	1 (0.2)	9 (2.1)	1 (0.2)	8 (3.8)	0
Dyspepsia	32 (7.6)	0	18 (4.2)	0	9 (4.2)	0
Abdominal pain upper	26 (6.2)	0	18 (4.2)	0	9 (4.2)	0
Mouth ulceration	20 (4.8)	0	12 (2.8)	1 (0.2)	8 (3.8)	0
Gingival bleeding	19 (4.5)	0	2 (0.5)	0	2 (0.9)	0
Abdominal pain	17 (4.0)	0	18 (4.2)	0	5 (2.3)	0
Anal fissure	17 (4.0)	0	0	0	2 (0.9)	0
Gastrooesophageal reflux disease	15 (3.6)	0	15 (3.5)	0	3 (1.4)	0
Gastritis	13 (3.1)	1 (0.2)	9 (2.1)	0	4 (1.9)	0
Dry mouth	10 (2.4)	0	10 (2.3)	0	4 (1.9)	0
Abdominal distension	5 (1.2)	0	9 (2.1)	0	4 (1.9)	0

*1 Incidence by PT is presented for adverse events reported by ≥2% of subjects in any group. *2 Any event of gastrointestinal disorder

[75)] Events in the MedDRA SOC "gastrointestinal disorders" were counted.

Table 58. Incidence of serious gastrointestinal disorders etc.[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Gastrointestinal disorders leading to death	0	0	0
Serious gastrointestinal disorders	21 (5.0)	7 (1.6)	4 (1.9)
Diarrhoea	4 (1.0)	2 (0.5)	1 (0.5)
Enterocolitis	2 (0.5)	0	0
Nausea	2 (0.5)	0	1 (0.5)
Gastrointestinal haemorrhage	0	2 (0.5)	0
Gastrointestinal disorders leading to treatment discontinuation[*2]	5 (1.2)	2 (0.5)	0
Gastrointestinal disorders leading to dose or infusion interruption[*2]	66 (15.7)	20 (4.7)	12 (5.6)
Diarrhoea	19 (4.5)	6 (1.4)	5 (2.3)
Stomatitis	13 (3.1)	4 (0.9)	2 (0.9)
Vomiting	9 (2.1)	2 (0.5)	4 (1.9)
Nausea	8 (1.9)	2 (0.5)	3 (1.4)
Abdominal pain	2 (0.5)	1 (0.2)	0
Dysphagia	2 (0.5)	1 (0.2)	0
Gastritis	2 (0.5)	1 (0.2)	0
Anal fissure	2 (0.5)	0	0
Anal rash	2 (0.5)	0	0
Cheilitis	2 (0.5)	0	0
Colitis	2 (0.5)	0	0
Constipation	2 (0.5)	0	0
Duodenal ulcer	2 (0.5)	0	0
Oesophagitis	2 (0.5)	0	0
Gastrointestinal disorders leading to dose reduction[*2]	26 (6.2)	4 (0.9)	4 (1.9)
Stomatitis	5 (1.2)	0	1 (0.5)
Diarrhoea	3 (0.7)	2 (0.5)	1 (0.5)
Nausea	3 (0.7)	1 (0.2)	0
Anal fissure	2 (0.5)	0	0
Anal inflammation	2 (0.5)	0	0
Cheilitis	2 (0.5)	0	0
Mouth ulceration	2 (0.5)	0	0
Vomiting	2 (0.5)	0	1 (0.5)

*1 Incidence by PT is presented for adverse events reported by ≥2 subjects in any group.
*2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 59 shows the details of patients with serious gastrointestinal disorders for which a causal relationship to Ami or Laz could not be ruled out [70)] in the MARIPOSA study, Study NSC1001, and Study EDI1001 and the details of patients with serious gastrointestinal disorders for which a causal relationship to Laz could not be ruled out [70)] in the clinical studies of Laz monotherapy.[73)]

Table 59. Listing of patients with serious gastrointestinal disorders for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Laz group)	8[redacted]	F	Diarrhoea	3	407	8	—	Dose interrupted	Resolved	Laz
	7[redacted]	F	Vomiting	3	52	6	—	Dose interrupted	Resolved	Laz
NSC2001 (Laz monotherapy)	6[redacted]	F	Dyspepsia	2	22	12	—	None	Resolved	Laz
	7[redacted]	F	Diarrhoea	3	8	2	—	Dose interrupted	Resolving	Laz
	6[redacted]	F	Gastritis	3	22	11	—	Dose interrupted	Resolving	Laz
YH25448-301 (Laz group)	7[redacted]	M	Diarrhoea	1	1	161	—	None	Not resolved	Laz
			Diarrhoea	3	162	6	—	None	Resolving	Laz
			Diarrhoea	1	168	2	—	Dose interrupted	Resolved	Laz
	7[redacted]	F	Vomiting	3	25	5	—	Dose interrupted	Resolving	Laz
			Vomiting	1	30	25	—	None	Not resolved	Laz
			Vomiting	3	55	4	—	Dose reduced	Resolving	Laz
			Vomiting	1	59	21	—	None	Resolved	Laz
	6[redacted]	M	Diarrhoea	2	356	23	—	None	Resolving	Laz
			Diarrhoea	1	379	6	—	None	Not resolved	Laz
			Diarrhoea	3	385	40	—	Dose interrupted	Resolving	Laz
			Diarrhoea	1	425	80	—	Dose reduced	Resolved	Laz
	8[redacted]	F	Diarrhoea	2	39	19	—	None	Resolved	Laz
			Diarrhoea	3	338	3	—	Dose interrupted	Resolved	Laz
MARIPOSA (Ami/Laz group)	6[redacted]	M	Haemorrhoidal haemorrhage	2	149	3	None	Dose interrupted	Resolved	Laz
			Intestinal haemorrhage	2	149	6	None	Dose interrupted	Resolved	Laz
	6[redacted]	F	Nausea	2	524	4	None	Dose interrupted	Resolved	Laz
	6[redacted]	M	Vomiting	3	162	25	Dose interrupted	None	Resolving	Ami and Laz
			Colitis	4	171	17	Dose interrupted	None	Resolved	Ami and Laz
	6[redacted]	F	Diarrhoea	3	147	18	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	7[redacted]	F	Diarrhoea	3	23	13	Dose reduced	Dose interrupted	Resolving	Ami and Laz
	6[redacted]	F	Gastritis	3	158	Unknown	None	Dose interrupted	Not resolved	Ami and Laz
	6[redacted]	F	Nausea	3	15	7	Dose interrupted	Dose reduced	Resolved	Ami and Laz
	8[redacted]	F	Diarrhoea	3	72	2	None	Dose interrupted	Resolved	Ami and Laz
			Diarrhoea	3	87	5	Discontinued	Dose interrupted	Resolved	Ami and Laz
	6[redacted]	M	Diarrhoea	3	12	5	None	None	Resolved	Ami and Laz
			Diarrhoea	3	27	4	Dose interrupted	Dose interrupted	Resolving	Ami and Laz

NSC1001 (Ami/Laz*)	7[redacted]	F	Diarrhoea	3	260	7	Discontinued	Dose interrupted	Resolved	Ami
			Diarrhoea	3	405	6	Not applicable	Dose interrupted	Resolved	Laz
			Colitis	3	419	10	Not applicable	Dose interrupted	Resolved	Laz
	6[redacted]	F	Gastric perforation	4	51	120	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
	6[redacted]	F	Pancreatitis acute	4	23	7	None	None	Resolved	Ami and Laz
	4[redacted]	M	Nausea	2	9	3	None	None	Resolving	Ami and Laz
			Nausea	1	11	Unknown	None	None	Not resolved	Ami and Laz
	7[redacted]	F	Stomatitis	3	40	56	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	6[redacted]	F	Nausea	3	29	6	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
EDI1001 (Ami/Laz cohort)	3[redacted]	F	Vomiting	2	177	4	None	None	Resolved	Ami and Laz
	6[redacted]	M	Stomatitis	2	12	39	Dose interrupted	None	Resolving	Ami and Laz

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

PMDA's view:

Given that multiple cases of serious diarrhoea whose causal relationship to Laz could be rationally explained were reported in the clinical studies of Laz including the MARIPOSA study, and that diarrhoea is a known risk associated with the existing EGFR-TKIs, attention should be paid to the possible occurrence of serious diarrhoea following administration of Laz. Thus, the applicant should appropriately advise healthcare professionals in clinical practice about the incidence and management of serious diarrhoea in the clinical studies, using the Laz package insert and other materials.

7.R.3.8 Skin disorders (including paronychia)

The applicant's explanation about skin disorders (including paronychia)[76] associated with Laz:

The incidence of skin disorders (including paronychia) in the MARIPOSA study is shown in Table 60 and Table 61. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of skin disorder (including paronychia) (min., max.) (days) were 144 (1, 938), 141 (1, 919), and 121 (1, 833), respectively.

[76] Events in the MedDRA SOC "skin and subcutaneous tissue disorders" and events coded to the MedDRA PT "paronychia" were counted.

Table 60. Incidence of skin disorders (including paronychia)[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders (including paronychia)[*2]	395 (93.8)	151 (35.9)	293 (68.5)	9 (2.1)	166 (77.9)	8 (3.8)
Paronychia	288 (68.4)	46 (10.9)	121 (28.3)	2 (0.5)	61 (28.6)	2 (0.9)
Rash	260 (61.8)	65 (15.4)	131 (30.6)	3 (0.7)	95 (44.6)	4 (1.9)
Dermatitis acneiform	122 (29.0)	35 (8.3)	55 (12.9)	0	45 (21.1)	0
Pruritus	99 (23.5)	2 (0.5)	73 (17.1)	1 (0.2)	36 (16.9)	0
Dry skin	67 (15.9)	1 (0.2)	60 (14.0)	1 (0.2)	38 (17.8)	0
Skin fissures	40 (9.5)	3 (0.7)	23 (5.4)	0	5 (2.3)	0
Rash maculo-papular	27 (6.4)	4 (1.0)	8 (1.9)	0	8 (3.8)	0
Palmar-plantar erythrodysaesthesia syndrome	24 (5.7)	1 (0.2)	15 (3.5)	0	13 (6.1)	2 (0.9)
Skin ulcer	22 (5.2)	3 (0.7)	2 (0.5)	0	4 (1.9)	0
Skin lesion	19 (4.5)	4 (1.0)	5 (1.2)	0	2 (0.9)	0
Acne	18 (4.3)	1 (0.2)	7 (1.6)	0	3 (1.4)	0
Erythema	16 (3.8)	0	4 (0.9)	0	4 (1.9)	0
Alopecia	15 (3.6)	0	20 (4.7)	0	27 (12.7)	0
Nail disorder	15 (3.6)	1 (0.2)	13 (3.0)	0	4 (1.9)	0
Hypertrichosis	12 (2.9)	0	0	0	1 (0.5)	
Hirsutism	11 (2.6)	0	0	0	1 (0.5)	
Decubitus ulcer	9 (2.1)	1 (0.2)	4 (0.9)	0	1 (0.5)	0
Dermatitis	9 (2.1)	2 (0.5)	11 (2.6)	0	3 (1.4)	0
Onycholysis	9 (2.1)	1 (0.2)	8 (1.9)	0	2 (0.9)	0
Rash pruritic	9 (2.1)	0	4 (0.9)	0	6 (2.8)	0
Onychoclasis	4 (1.0)	0	6 (1.4)	0	6 (2.8)	0
Eczema	5 (1.2)	0	5 (1.2)	0	5 (2.3)	0
Urticaria	5 (1.2)	0	7 (1.6)	0	5 (2.3)	0

*1 Incidence by PT is presented for adverse events reported by ≥2% of subjects in any group. *2 Any event of skin disorder

Table 61. Incidence of serious skin disorders (including paronychia) etc.[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Skin disorders (including paronychia) leading to death	0	0	0
Serious skin disorders (including paronychia)	11 (2.6)	0	0
Rash	7 (1.7)	0	0
Decubitus ulcer	1 (0.2)	0	0
Dermatitis	1 (0.2)	0	0
Dermatitis acneiform	1 (0.2)	0	0
Drug eruption	1 (0.2)	0	0
Skin disorders (including paronychia) leading to treatment discontinuation[*2]	34 (8.1)	0	1 (0.5)
Paronychia	14 (3.3)	0	1 (0.5)
Rash	11 (2.6)	0	0
Dermatitis acneiform	6 (1.4)	0	0
Skin lesion	3 (0.7)	0	0
Skin fissures	2 (0.5)	0	0
Skin ulcer	2 (0.5)	0	0
Skin disorders (including paronychia) leading to dose or infusion interruption[*2]	232 (55.1)	17 (4.0)	20 (9.4)
Rash	104 (24.7)	4 (0.9)	9 (4.2)
Paronychia	91 (21.6)	4 (0.9)	4 (1.9)
Dermatitis acneiform	50 (11.9)	1 (0.2)	3 (1.4)
Skin ulcer	10 (2.4)	0	0
Rash maculo-papular	9 (2.1)	0	0
Skin fissures	8 (1.9)	0	0
Palmar-plantar erythrodysaesthesia syndrome	7 (1.7)	1 (0.2)	2 (0.9)
Pruritus	6 (1.4)	3 (0.7)	2 (0.9)
Skin lesion	6 (1.4)	0	0
Acne	3 (0.7)	0	0
Dermatitis	3 (0.7)	2 (0.5)	0
Decubitus ulcer	2 (0.5)	0	0
Drug eruption	2 (0.5)	1 (0.2)	1 (0.5)
Erythema	2 (0.5)	0	0
Onycholysis	2 (0.5)	0	0
Rash erythematous	2 (0.5)	0	0
Skin exfoliation	2 (0.5)	0	0
Skin disorders (including paronychia) leading to dose reduction[*2]	190 (45.1)	3 (0.7)	5 (2.3)
Rash	84 (20.0)	2 (0.5)	3 (1.4)
Paronychia	80 (19.0)	1 (0.2)	0
Dermatitis acneiform	38 (9.0)	0	0
Rash maculo-papular	6 (1.4)	0	0
Skin lesion	5 (1.2)	0	0
Dry skin	4 (1.0)	0	0
Skin fissures	4 (1.0)	0	0
Palmar-plantar erythrodysaesthesia syndrome	3 (0.7)	0	2 (0.9)
Pruritus	3 (0.7)	1 (0.2)	0
Dermatitis	2 (0.5)	0	0
Skin exfoliation	2 (0.5)	0	0

*1 Incidence by PT is presented for adverse events reported by ≥2 subjects in any group.
*2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 62 shows the details of patients with serious skin disorders for which a causal relationship to Ami or Laz could not be ruled out[70)] following administration of Ami/Laz in the MARIPOSA study, Study NSC1001, and Study EDI1001. No serious skin disorders for which a causal relationship to Laz could not be ruled out were reported in the clinical studies of Laz monotherapy.[73)]

Table 62. Listing of patients with serious skin disorders (including paronychia) for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Ami/Laz group)	6[redacted]	M	Rash	3	37	22	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	4[redacted]	M	Rash	3	40	29	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	6[redacted]	M	Rash	1	107	Unknown	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz
	7[redacted]	M	Drug eruption	3	206	33	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	6[redacted]	F	Rash	3	66	14	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
			Rash	3	149	16	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
			Rash	2	164	3	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	M	Rash	3	399	23	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	6[redacted]	F	Rash	3	345	17	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	M	Dermatitis	3	240	14	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	6[redacted]	M	Dermatitis acneiform	3	185	41	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	F	Rash	3	22	20	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
NSC1001 (Ami/Laz*)	3[redacted]	F	Dermatitis acneiform	3	293	9	None	Dose interrupted	Resolving	Ami and Laz
	5[redacted]	M	Rash	3	34	27	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
			Rash	1	60	49	Not applicable	Not applicable	Resolved	Ami and Laz
	6[redacted]	F	Rash	3	56	12	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	7[redacted]	F	Paronychia	2	26	Unknown	None	None	Not resolved	Ami and Laz
	6[redacted]	F	Rash	3	92	23	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
	6[redacted]	F	Rash	3	142	10	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	5[redacted]	M	Paronychia	3	84	15	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
	6[redacted]	F	Dermatitis acneiform	2	352	68	Dose interrupted	Dose reduced	Not resolved	Ami and Laz
			Paronychia	2	352	110	Dose interrupted	Dose reduced	Not resolved	Ami and Laz
	7[redacted]	F	Dermatitis acneiform	3	112	16	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
EDI1001 (Ami/Laz cohort)	7[redacted]	F	Dermatitis	3	161	21	Not applicable	Not applicable	Resolved	Ami and Laz
	6[redacted]	M	Dermatitis acneiform	3	183	15	Dose interrupted	Dose interrupted	Resolving	Ami

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

In the clinical studies of Ami/Laz or Laz monotherapy including the MARIPOSA study,[73] particularly severe skin disorders, i.e., toxic epidermal necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome), were not reported.

In the MARIPOSA study, the following was recommended for the prophylaxis of skin disorders:

- Avoid exposure to sunlight.
- Wear hat, sunglasses, etc.

- Use broad-spectrum sunscreen containing zinc oxide or titanium dioxide with a skin protection factor (SPF) of ≥30.
- Apply alcohol-free emollient cream etc.

The MARIPOSA protocol recommended that patients in the Ami/Laz group should begin topical and oral antibiotic therapy on Cycle 1 Day 1 and continue the therapy for the first 8 weeks. In the MARIPOSA study, the proportions of patients who were prescribed either topical or oral antibiotics for the prevention of skin disorders at baseline were 22.3% (94 of 421 subjects) in the Ami/Laz group, 6.1% (26 of 428 subjects) in the Osi group, and 8.9% (19 of 213 subjects) in the Laz group.

PMDA's view:
Given the following points, attention should be paid to the possible occurrence of skin disorders following administration of Laz. Thus, the applicant should appropriately provide information on the incidence of skin disorders in the clinical studies of Laz monotherapy to healthcare professionals in clinical practice, using the Laz package insert and other materials.

- Given that Laz is a drug targeting EGFR, and that EGFR is widely expressed in the skin tissues such as the basal layer of the epidermis, the outer root sheath, and the eccrine and sebaceous glands (*Journal of clinical therapeutics & medicine*. 2016; 32: 941-9), Laz is considered to affect the skin extensively.
- Serious skin disorders are a known risk associated with the existing EGFR-TKIs.
- In the MARIPOSA study, the incidence of Grade ≥3 skin disorders tended to be higher in the Laz group than in the Osi group (Toxic epidermal necrolysis, oculomucocutaneous syndrome, and erythema multiforme are important identified risks of Osi) (see "RMP for Tagrisso Tablets 40 mg and Tagrisso Tablets 80 mg as of July 12, 2024").

7.R.3.9 Cardiac failure

The applicant's explanation about cardiac failure[77)] associated with Laz or Ami/Laz:
The incidence of cardiac failure in the MARIPOSA study is shown in Table 63 and Table 64. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of cardiac failure (min., max.) (days) were 254 (25, 728), 198 (61, 842), and 253 (84, 738), respectively.

[77)] Events in the MedDRA SMQ "cardiac failure (narrow)" were counted.

Table 63. Incidence of cardiac failure (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac failure*	28 (6.7)	9 (2.1)	26 (6.1)	9 (2.1)	9 (4.2)	4 (1.9)
Ejection fraction decreased	18 (4.3)	2 (0.5)	20 (4.7)	4 (0.9)	8 (3.8)	3 (1.4)
Cardiac failure	5 (1.2)	2 (0.5)	7 (1.6)	6 (1.4)	3 (1.4)	1 (0.5)
Pulmonary oedema	2 (0.5)	2 (0.5)	0	0	0	0
Cardiac failure acute	1 (0.2)	1 (0.2)	0	0	0	0
Cardiac failure chronic	1 (0.2)	1 (0.2)	0	0	0	0
Cardiopulmonary failure	1 (0.2)	1 (0.2)	0	0	0	0
Cardiac failure congestive	1 (0.2)	0	1 (0.2)	0	0	0

*Any event of cardiac failure

Table 64. Incidence of serious cardiac failure etc.[*1] (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Cardiac failure leading to death	1 (0.2)	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0	0
Cardiac failure	0	1 (0.2)	0
Serious cardiac failure	3 (0.7)	5 (1.2)	1 (0.5)
Cardiac failure	1 (0.2)	5 (1.2)	1 (0.5)
Cardiopulmonary failure	1 (0.2)	0	0
Pulmonary oedema	1 (0.2)	0	0
Cardiac failure leading to treatment discontinuation*	5 (1.2)	3 (0.7)	0
Ejection fraction decreased	2 (0.5)	2 (0.5)	0
Cardiac failure	1 (0.2)	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0	0
Pulmonary oedema	1 (0.2)	0	0
Cardiac failure leading to dose or infusion interruption*	10 (2.4)	14 (3.3)	4 (1.9)
Ejection fraction decreased	8 (1.9)	11 (2.6)	4 (1.9)
Cardiac failure	1 (0.2)	3 (0.7)	1 (0.5)
Cardiac failure acute	1 (0.2)	0	0
Cardiac failure leading to dose reduction*	1 (0.2)	2 (0.5)	1 (0.5)
Ejection fraction decreased	1 (0.2)	2 (0.5)	1 (0.5)

*Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 65 shows the details of a patient with serious cardiac failure for which a causal relationship to Ami or Laz could not be ruled out[70)] in the clinical studies of Ami/Laz or Laz monotherapy including the MARIPOSA study.[73)]

Table 65. Listing of patient with serious cardiac failure for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Ami/Laz group)	7[redacted]	M	Cardiac failure	4	78	Unknown	Discontinued	Discontinued	Not resolved	Ami and Laz

PMDA's view:

Given the following points, attention should be paid to the possible occurrence of cardiac failure following administration of Laz. Thus, the applicant should appropriately provide information on the incidence of cardiac

failure in the clinical studies of Laz monotherapy to healthcare professionals in clinical practice, using the Laz package insert and other materials.

- Cardiac failure has been reported with the existing EGFR-TKIs.
- In the MARIPOSA study, the incidence of Grade ≥3 cardiac failure in the Laz group was similar to that in the Osi group (Cardiac failure is an important identified risk of Osi) (see RMP for Tagrisso Tablets 40 mg and Tagrisso Tablets 80 mg as of July 12, 2024").

7.R.3.10 Eye disorders

The applicant's explanation about eye disorders[78] associated with Laz or Ami/Laz:

The incidence of eye disorders in the MARIPOSA study is shown in Table 66 and Table 67. In the Ami/Laz, Osi, and Laz groups of the MARIPOSA study, the median times to the first onset of eye disorder (min., max.) (days) were 128.0 (1, 777), 241.0 (3, 812), and 254.0 (1, 756), respectively.

Table 66. Incidence of eye disorders*1 (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders*2	133 (31.6)	6 (1.4)	63 (14.7)	2 (0.5)	32 (15.0)	1 (0.5)
Dry eye	37 (8.8)	1 (0.2)	18 (4.2)	0	7 (3.3)	0
Cataract	17 (4.0)	2 (0.5)	12 (2.8)	1 (0.2)	2 (0.9)	1 (0.5)
Blepharitis	15 (3.6)	0	6 (1.4)	0	0	0
Vision blurred	12 (2.9)	0	6 (1.4)	0	6 (2.8)	0
Keratitis	11 (2.6)	2 (0.5)	2 (0.5)	0	1 (0.5)	0
Lacrimation increased	9 (2.1)	0	0	0	3 (1.4)	0
Ocular hyperaemia	8 (1.9)	1 (0.2)	2 (0.5)	0	0	0
Conjunctival haemorrhage	6 (1.4)	0	3 (0.7)	0	1 (0.5)	0
Conjunctival hyperaemia	6 (1.4)	0	0	0	0	0
Eye pruritus	6 (1.4)	0	1 (0.2)	0	1 (0.5)	0
Trichomegaly	6 (1.4)	0	0	0	1 (0.5)	0
Eye discharge	5 (1.2)	0	0	0	1 (0.5)	0
Eyelid oedema	5 (1.2)	0	0	0	0	0
Xerophthalmia	5 (1.2)	0	0	0	1 (0.5)	0
Conjunctivitis allergic	4 (1.0)	0	2 (0.5)	0	0	0
Visual acuity reduced	4 (1.0)	0	0	0	3 (1.4)	0
Visual impairment	3 (0.7)	0	4 (0.9)	0	4 (1.9)	0

*1 Incidence by PT is presented for adverse events reported by ≥1% of subjects in any group. *2 Any event of eye disorder

[78] Events in the MedDRA SOC "eye disorders" were counted.

Table 67. Incidence of serious eye disorders etc. (MARIPOSA study)

PT (MedDRA ver.25.0)	n (%)		
	Ami/Laz N = 421	Osi N = 428	Laz N = 213
Eye disorders leading to death	0	0	0
Serious eye disorders	2 (0.5)	0	1 (0.5)
Giant papillary conjunctivitis	1 (0.2)	0	0
Keratitis	1 (0.2)	0	0
Papilloedema	1 (0.2)	0	0
Optic atrophy	0	0	1 (0.5)
Optic ischaemic neuropathy	0	0	1 (0.5)
Eye disorders leading to treatment discontinuation *	1 (0.2)	0	1 (0.5)
Blepharitis	1 (0.2)	0	0
Optic atrophy	0	0	1 (0.5)
Optic ischaemic neuropathy	0	0	1 (0.5)
Eye disorders leading to dose or infusion interruption *	9 (2.1)	2 (0.5)	0
Ocular hyperaemia	3 (0.7)	0	0
Blepharitis	2 (0.5)	0	0
Cataract	1 (0.2)	0	0
Dry eye	1 (0.2)	0	0
Giant papillary conjunctivitis	1 (0.2)	0	0
Keratitis	1 (0.2)	0	0
Periorbital oedema	1 (0.2)	0	0
Visual acuity reduced	1 (0.2)	0	0
Amaurosis fugax	0	1 (0.2)	0
Glaucoma	0	1 (0.2)	0
Eye disorders leading to dose reduction*	3 (0.7)	0	0
Blepharitis	1 (0.2)	0	0
Papilloedema	1 (0.2)	0	0
Vision blurred	1 (0.2)	0	0

*Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 68 shows the details of patients with serious eye disorders for which a causal relationship to Ami or Laz could not be ruled out[70)] in the clinical studies of Ami/Laz or Laz monotherapy including the MARIPOSA study.[73)]

Table 68. Listing of patients with serious eye disorders for which a causal relationship to Ami or Laz could not be ruled out

Study ID	Age	Sex	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with Ami	Action taken with Laz	Outcome	Study drug for which causal relationship to the event could not be ruled out
MARIPOSA (Laz group)	6[redacted]	F	Optic atrophy	3	456	Unknown	—	Discontinued	Not resolved	Laz
			Optic ischaemic neuropathy	3	486	Unknown	—	Discontinued	Not resolved	Laz
MARIPOSA (Ami/Laz group)	7[redacted]	M	Keratitis	3	463	33	Dose interrupted	None	Resolving	Ami
			Giant papillary conjunctivitis	3	485	11	Dose interrupted	None	Resolving	Ami
NSC1001 (Ami/Laz*)	7[redacted]	F	Corneal erosion	3	127	3	Dose interrupted	Dose interrupted	Resolving	Ami and Laz
			Corneal erosion	3	179	3	Dose interrupted	Dose interrupted	Resolved	Ami and Laz
			Corneal erosion	3	277	42	Dose interrupted	Discontinued	Resolved	Ami and Laz
	7[redacted]	F	Ulcerative keratitis	3	72	14	Dose interrupted	Dose interrupted	Not resolved	Ami and Laz

*Japanese phase Ib part and Ami/Laz cohort A of Global phase Ib part

PMDA's view:

Given the following points, the applicant should appropriately provide information on the incidence of corneal disorders in the clinical studies to healthcare professionals in clinical practice, using the Laz package insert and other materials, and collect post-marketing information. If any new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

- Corneal disorders have been reported with the existing EGFR-TKIs.
- In repeated-dose toxicity studies in rats and dogs, corneal effects occurred at dose levels corresponding to exposure levels close to the human exposure [see Section 5.2.2].

7.R.4 Clinical positioning and indications

The indications and precautions concerning indications for Ami (the present partial change application) and Laz (the present application), as proposed by the applicant, are shown in the table below.

	Indications	Precautions Concerning Indications
Ami*	● *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC ● *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation, etc., in patients enrolled in the clinical study and of the efficacy and safety of Ami. ● Ami should be used in patients with an *EGFR* exon 20 insertion mutation or an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
Laz	*EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Laz in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of Laz. ● Laz should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.

* Underline denotes additions to the approved labeling.

PMDA's conclusion:

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following considerations, the statements in the table below should be included in the PRECAUTIONS CONCERNING INDICATIONS sections for Ami and Laz, and then the proposed indications should be included in the INDICATIONS sections for Ami and Laz.

	Indications	Precautions Concerning Indications
Ami*	● *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC ● *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation, etc., in patients enrolled in the clinical study and of the efficacy and safety of Ami. ● Ami should be used in patients with an *EGFR* exon 20 insertion mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing. [*EGFR* mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Ami should be used in patients with an *EGFR* mutation (excluding *EGFR* exon 20 insertion mutations) as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
Laz	*EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Laz in the neoadjuvant or adjuvant setting have not been established. ● Laz should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.

* Underline denotes additions to the approved labeling.

7.R.4.1 Clinical positioning of Ami/Laz and target population

Ami/Laz for patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy is described as follows in the major Japanese and foreign clinical practice guidelines and textbook of clinical oncology.[79)]

[Clinical practice guidelines]

- NCCN guidelines (NSCLC) (v.1.2025)
  - Ami/Laz is strongly recommended as first-line therapy for patients with *EGFR* mutation (Ex19del or L858R)-positive unresectable advanced or recurrent NSCLC. If *EGFR* mutation (Ex19del or L858R) is discovered during systemic therapy, interruption of the current therapy for switching to Osi or Ami/Laz is recommended as a treatment option for patients with unresectable advanced or recurrent NSCLC.

[Textbook]

- DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (12th ed., J.B.Lippencott Company, 2023, USA)
  - The MARIPOSA study compared Ami/Laz, Osi, and Laz as first-line treatment in 1,074 patients with *EGFR* mutation (Ex19del or L858R)-positive unresectable advanced or recurrent NSCLC. The results showed the superiority of Ami/Laz over Osi in PFS and a trend in favor of Ami/Laz in OS. Laz showed comparable efficacy to Osi.

The applicant's explanation about the clinical positioning of Ami/Laz and the target population:
The MARIPOSA study in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy demonstrated the clinical usefulness of Ami/Laz [see Sections 7.R.2 and 7.R.3]. Thus, Ami/Laz should be positioned as a treatment option for these patients.

There are no data from clinical studies that evaluated the efficacy and safety of (1) Ami/Laz as neoadjuvant or adjuvant therapy for NSCLC or (2) Ami/Laz in (i) patients without documented *EGFR* Ex19del or L858R mutations or (ii) patients previously treated with chemotherapy, i.e. the patient populations not included in the MARIPOSA study. Thus, Ami/Laz is not recommended for the above (1) or (2).

In addition, patients with Ex19del or L858R mutations, as detected by testing performed by a certified or accredited local laboratory, were enrolled in the MARIPOSA study. As of May 7, 2024, Roche Diagnostics submitted a partial change application for a companion diagnostic, "the Cobas EGFR Mutation Test v2.0," as an aid in identifying patients eligible for treatment with Ami/Laz, and "the Cobas EGFR Mutation Test v2.0" should be used for selection of eligible patients for treatment with Ami/Laz.

Based on the above, the information on the patient population included in the MARIPOSA study [(1) patients with documented *EGFR* Ex19del or L858R mutations and (2) patients previously untreated with

[79)] NCCN guidelines (NSCLC) (v.1.2025), NCI-PDQ (August 30, 2024), ESMO guideline (2023), Japanese clinical practice guideline (2024), DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (12th ed., J.B.Lippencott Company, 2023, USA), New Clinical Oncology (the 7th edition, Nankodo), etc.

chemotherapy] was included in the CLINICAL STUDIES section of the package insert, and then the statements in the table below were included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for Ami and Laz. In the PRECAUTIONS CONCERNING INDICATIONS section for Ami, underlined texts were added to the initially approved labeling, and the above (1) and (2) were both reflected in the phrase "the type of genetic mutation, etc." in the initially approved labeling.

	Indications	Precautions Concerning Indications
Ami*	● *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC ● *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation, etc., in patients enrolled in the clinical study and of the efficacy and safety of Ami. ● Ami should be used in patients with an *EGFR* exon 20 insertion mutation or an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
Laz	*EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Laz in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of Laz. ● Laz should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.

* Underline denotes additions to the approved labeling.

The applicant's explanation about when to use Ami/Laz and when to use (1) EGFR-TKIs or (2) Osi in combination with platinum and pemetrexed sodium hydrate (PEM), which have been approved for the indication of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC in Japan:

(1) EGFR-TKIs

Given that EGFR-TKIs for *EGFR* mutation-positive NSCLC previously untreated with chemotherapy are described as follows in the Japanese and foreign clinical practice guidelines, and that the MARIPOSA study demonstrated the superiority of Ami/Laz over Osi in the primary endpoint of PFS as assessed by BICR, Ami/Laz should be preferred over the existing EGFR-TKIs.

- The Japanese clinical practice guideline (2024) strongly recommends Osi and includes no recommendations for other EGFR-TKIs.
- According to the NCCN guidelines (NSCLC) (v.10.2024), the "preferred" therapy is Osi, and "other recommended" therapies are other EGFR-TKIs.
- According to the ESMO guideline (2023), Osi is the preferable first-line treatment option, and third-generation EGFR-TKIs are still one standard first-line treatment.

(2) Osi in combination with platinum and PEM

Given that there are no data from clinical studies that compared the efficacy and safety of Osi in combination with platinum and PEM vs. Ami/Laz, etc., when to use Osi in combination with platinum and PEM and when to use Ami/Laz are unknown. Treatment will be chosen with an understanding of the efficacy and safety of the individual agents, according to individual patients' conditions.

PMDA’s view:

PMDA largely accepted the applicant's explanation. However, PMDA made the following conclusions regarding the PRECAUTIONS CONCERNING INDICATIONS section.

- While information on the type of genetic mutation in patients enrolled in the MARIPOSA study should be included in the CLINICAL STUDIES section of the package insert, given that Ami/Laz will be used in patients with an *EGFR* mutation, as detected by a companion diagnostic etc., under supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy, there is little need to include the following statement in the PRECAUTIONS CONCERNING INDICATIONS section: "Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section of the package insert."
- Given that Ami/Laz will be used by physicians with sufficient knowledge of and experience in cancer chemotherapy, there is no need to include the following statement in the PRECAUTIONS CONCERNING INDICATIONS section: "Patients previously untreated with chemotherapy were enrolled in the MARIPOSA study."

Based on the above discussion etc., the statements in the table below should be included in the PRECAUTIONS CONCERNING INDICATIONS sections for Ami and Laz, and then the proposed indication of "*EGFR* mutation-positive unresectable advanced or recurrent NSCLC" is appropriate for Ami and Laz.

	Indications	Precautions Concerning Indications
Ami*	● *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC ● *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation, etc., in patients enrolled in the clinical study and of the efficacy and safety of Ami. ● Ami should be used in patients with an *EGFR* exon 20 insertion mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing. [*EGFR* mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Ami should be used in patients with an *EGFR* mutation (excluding *EGFR* exon 20 insertion mutations) as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
Laz	*EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Laz in the neoadjuvant or adjuvant setting have not been established. ● Laz should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.

* Underline denotes additions to the approved labeling.

A partial change application for a companion diagnostic etc., "the Cobas EGFR Mutation Test v2.0," as an aid in identifying patients eligible for treatment with Ami/Laz, was submitted. The appropriateness of the use of "the Cobas EGFR Mutation Test v2.0" for selection of eligible patients for treatment with Ami/Laz will be described in the Review Report (2).

7.R.4.2 Use of Ami/Laz in patients aged ≥65 years

According to the results of an additional ad hoc analysis of OS (data cutoff date of May 13, 2024) for subgroups in the MARIPOSA study, the point estimate of the hazard ratio of OS was >1 in patients aged ≥65 years. PMDA asked the applicant to explain the efficacy and safety of Ami/Laz by age group and the target population for Ami/Laz.

The applicant's response:

(1) Efficacy

The results of the final analysis of PFS (data cutoff date of August 11, 2023) and the Kaplan-Meier curves by age group (Table 69 and Figure 10, respectively) and the results of an additional ad hoc analysis of OS (data cutoff date of May 13, 2024) and the Kaplan-Meier curves by age group (Table 70 and Figure 11, respectively) in the MARIPOSA study are shown below.

Table 69. Results of final analysis of PFS by age group (BICR, FAS, data cutoff date of August 11, 2023)

Age group	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
<65 years	Ami/Laz	235	94 (40.0)	－ [20.47, －]	0.50 [0.39, 0.65]
	Osi	237	153 (64.6)	14.75 [12.91, 16.59]	
≥65 and <75 years	Ami/Laz	143	71 (49.7)	18.43 [14.55, 25.76]	1.19 [0.85, 1.67]
	Osi	139	67 (48.2)	22.14 [16.95, 27.50]	
≥75 years	Ami/Laz	51	27 (52.9)	20.30 [16.46, －]	0.77 [0.46, 1.30]
	Osi	53	32 (60.4)	15.90 [11.17, 20.40]	

－, Not estimable, *Unstratified Cox proportional hazards model

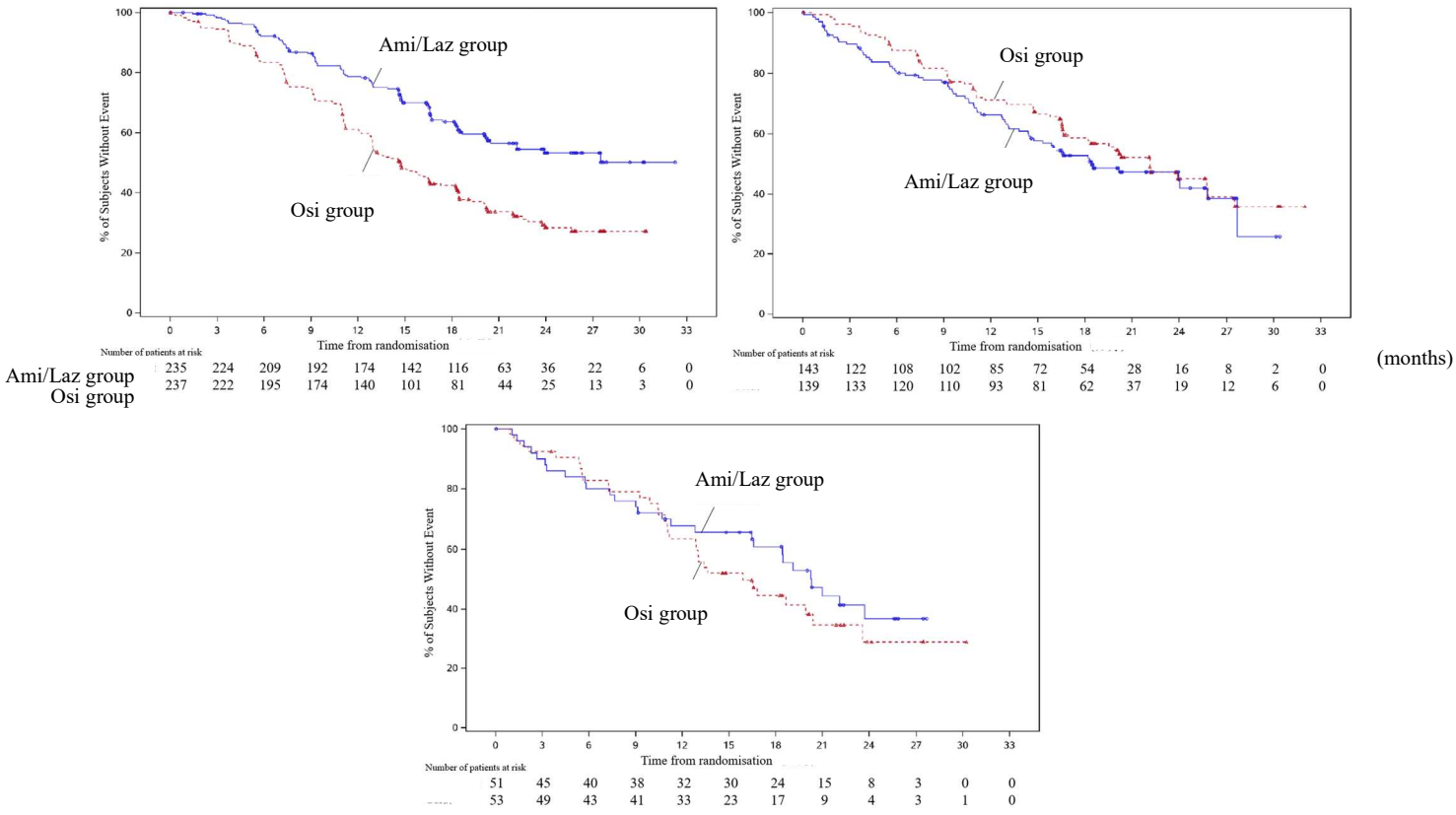

Figure 10. Kaplan-Meier curves of PFS at the time of final analysis by age group (BICR, FAS, data cutoff date of August 11, 2023)
(Left upper figure, <65 years; Right upper figure, ≥65 and <75 years; Lower figure, ≥75 years)

Table 70. Results of additional ad hoc analysis of OS by age group (FAS, data cutoff date of May 13, 2024)

Age group	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
<65 years	Ami/Laz	235	59 (25.1)	－ [－, －]	0.51 [0.37, 0.70]
	Osi	237	102 (43.0)	36.86 [30.62, －]	
≥65 and <75 years	Ami/Laz	143	61 (42.7)	－ [29.14, －]	1.33 [0.91, 1.92]
	Osi	139	51 (36.7)	－ [34.63, －]	
≥75 years	Ami/Laz	51	22 (43.1)	36.01 [23.85, －]	0.93 [0.52, 1.66]
	Osi	53	24 (45.3)	－ [23.36, －]	

－, Not estimable, *Unstratified Cox proportional hazards model

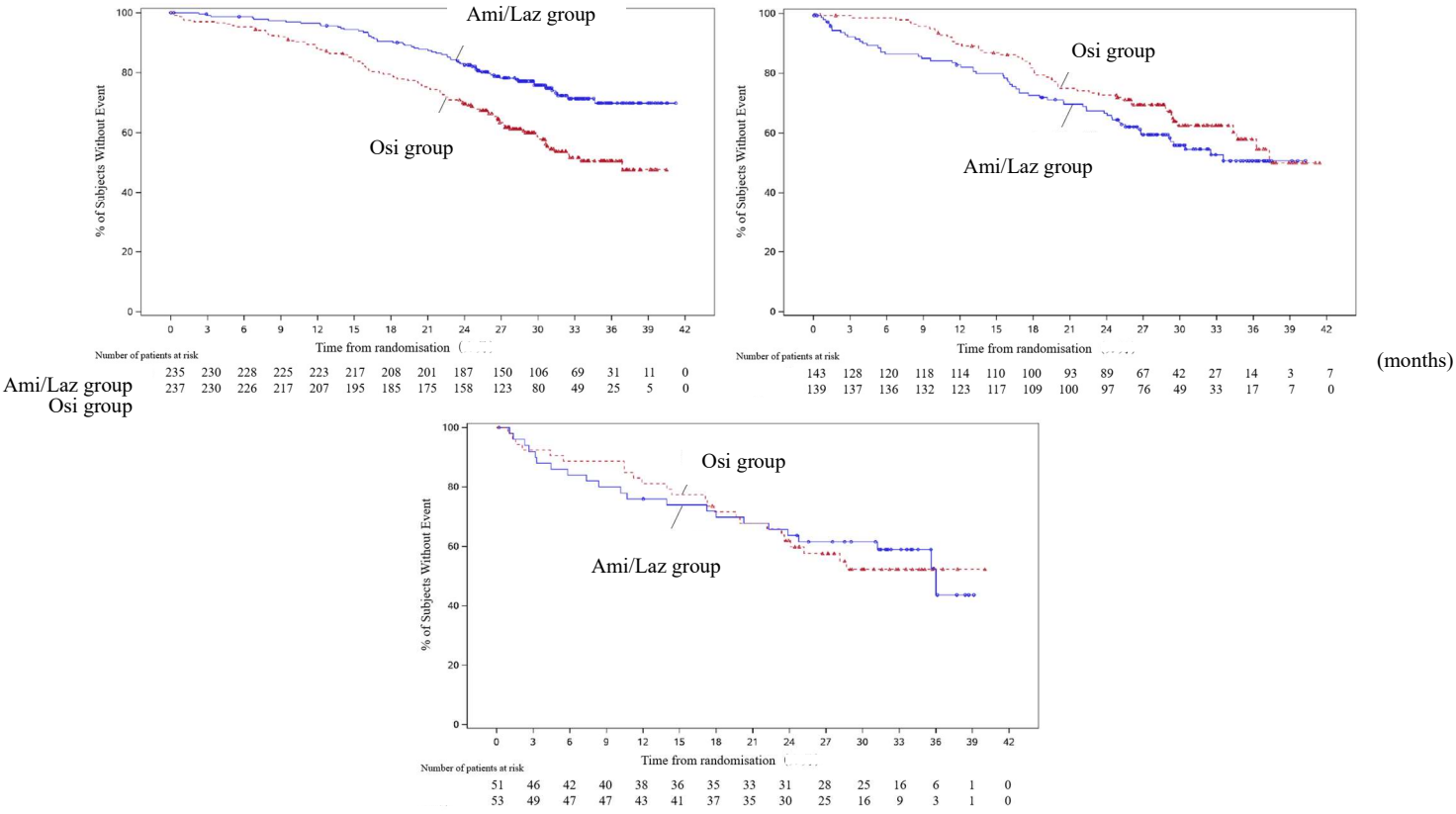

Figure 11. Kaplan-Meier curves of OS at the time of additional ad hoc analysis by age group (FAS, data cutoff date of May 13, 2024)
(Left upper figure, <65 years; Right upper figure, ≥65 and <75 years, Lower figure, ≥75 years)

The hazard ratios of PFS and OS for Ami/Laz vs. Osi tended to be higher in (ii) patients aged ≥65 and <75 years and patients aged ≥75 years than in (i) patients aged <65 years. The reason for this trend may be a trend towards longer PFS and OS in the Osi group in the above patients (ii) than in the above patients (i). However, given that there were no clear imbalances in the major patient characteristics that are considered to affect the efficacy of Ami/Laz among the age groups or between the treatment groups within each age group, and taking account of the results of an analysis adjusted for the imbalances in patient characteristics between the treatment groups among patients aged ≥65 and <75 years,[80)] the reason for the above trend is unknown, and

[80)] An analysis adjusted for the imbalances in patient characteristics between the treatment groups among patients aged ≥65 and <75 years was performed because there were certain imbalances in these patient characteristics between the treatment groups, and these patient characteristics (sex, female; race, Asian; history of brain metastasis, no) were associated with a trend towards favorable outcomes in the Osi group in the overall population. The hazard ratio of OS [95% CI] was 1.32 [0.91, 1.93], which was not clearly different from the unadjusted hazard ratio.

this may have been incidental. Thus, the above results do not deny the efficacy of Ami/Laz in patients aged ≥65 years.

(2) Safety

Table 71 shows a summary of safety data from the MARIPOSA study by age group. In the Ami/Laz group, the incidences of adverse events leading to death, serious adverse events, and adverse events leading to study drug discontinuation tended to be higher in patients aged ≥65 and <75 years and patients aged ≥75 years than in patients aged <65 years. However, given the following points, Ami/Laz is tolerable also in patients aged ≥65 years. Except for age, there were no imbalances in patient characteristics between patients aged <65 years and patients aged ≥65 and <75 years or patients aged ≥75 years.

- Adverse events leading to death for which a causal relationship to study drug could not be ruled out occurred in 2 patients aged ≥65 and <75 years (sudden death; and coronary artery disease and myocardial infarction [1 patient each]) and 2 patients aged ≥75 years (myocardial infarction; and pneumonitis [1 patient each]). Except for 1 case of pneumonitis, all those events may have been due to complications or progressive disease in elderly patients with NSCLC.
- The above trend was observed for venous thromboembolism. While the limited number of patients received prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz in the MARIPOSA study, administration of prophylactic anticoagulation will be recommended after marketing [see Section 7.R.5.2].
- In patients aged ≥65 years with (i) arterial thromboembolism, (ii) respiratory failure, or (iii) sudden death or death, (i) the event may have been due to complications, (ii) the event may have been due to progressive disease, and (iii) detailed information on the cause of death is not available.

Table 71. Summary of safety data (MARIPOSA study, data cutoff date of August 11, 2023)

	n (%)					
	Ami/Laz			Osi		
	<65 years	≥65 and <75 years	≥75 years	<65 years	≥65 and <75 years	≥75 years
	N = 233	N = 139	N = 49	N = 237	N = 139	N = 52
All adverse events	233 (100)	139 (100)	49 (100)	234 (98.7)	139 (100)	52 (100)
Grade ≥3 adverse events	163 (70.0)	109 (78.4)	44 (89.8)	91 (38.4)	68 (48.9)	24 (46.2)
Adverse events leading to death	8 (3.4)	15 (10.8)	11 (22.4)	16 (6.8)	5 (3.6)	10 (19.2)
Those for which a causal relationship to study drug could not be ruled out[*1]	0	2 (1.4)	2 (4.1)	1 (0.4)	0	1 (1.9)
Serious adverse events	89 (38.2)	85 (61.2)	31 (63.3)	78 (32.9)	42 (30.2)	23 (44.2)
Those for which a causal relationship to study drug could not be ruled out [*1]	41 (17.6)	41 (29.5)	15 (30.6)	11 (4.6)	8 (5.8)	5 (9.6)
Adverse events leading to treatment discontinuation[*2]	59 (25.3)	59 (42.4)	29 (59.2)	30 (12.7)	13 (9.4)	15 (28.8)
Ami	58 (24.9)	58 (41.7)	29 (59.2)	—	—	—
Laz	28 (12.0)	40 (28.8)	17 (34.7)	—	—	—
Osi	—	—	—	30 (12.7)	13 (9.4)	15 (28.8)
Adverse events leading to dose or infusion interruption[*2]	217 (93.1)	122 (87.8)	43 (87.8)	82 (34.6)	58 (41.7)	25 (48.1)
Ami	213 (91.4)	116 (83.5)	41 (83.7)	—	—	—
Laz	171 (73.4)	91 (65.5)	37 (75.5)	—	—	—
Osi	—	—	—	82 (34.6)	58 (41.7)	25 (48.1)
Adverse events leading to dose reduction[*2]	147 (63.1)	76 (54.7)	26 (53.1)	13 (5.5)	5 (3.6)	5 (9.6)
Ami	114 (48.9)	57 (41.0)	22 (44.9)	—	—	—
Laz	102 (43.8)	53 (38.1)	21 (42.9)	—	—	—
Osi	—	—	—	13 (5.5)	5 (3.6)	5 (9.6)

—, Not applicable

*1 Adverse events for which a causal relationship to any study drug could not be ruled out

*2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 72. Serious adverse events etc. reported at a certain level of incidence* in any age group (MARIPOSA study, data cutoff date of November 17, 2023)

PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz			Osi		
	<65 years	≥65 and <75 years	≥75 years	<65 years	≥65 and <75 years	≥75 years
	N = 233	N = 139	N = 49	N = 237	N = 139	N = 52
Adverse events leading to death	8 (3.4)	15 (10.8)	12 (24.5)	17 (7.2)	5 (3.6)	10 (19.2)
Pneumonia	3 (1.3)	1 (0.7)	2 (4.1)	1 (0.4)	1 (0.7)	2 (3.8)
Respiratory failure	1 (0.4)	3 (2.2)	0	2 (0.8)	0	0
Sudden death	1 (0.4)	2 (1.4)	1 (2.0)	0	0	1 (1.9)
Death	0	3 (2.2)	0	1 (0.4)	0	1 (1.9)
Myocardial infarction	0	1 (0.7)	2 (4.1)	0	0	0
Pulmonary embolism	1 (0.4)	0	1 (2.0)	1 (0.4)	1 (0.7)	0
Septic shock	0	0	2 (4.1)	1 (0.4)	0	0
Acinetobacter sepsis	0	0	1 (2.0)	0	0	0
Acute respiratory distress syndrome	1 (0.4)	0	0	0	0	0
Arteriosclerosis coronary artery	1 (0.4)	0	0	0	0	0
COVID-19	0	0	1 (2.0)	1 (0.4)	1 (0.7)	1 (1.9)
COVID-19 pneumonia	0	1 (0.7)	0	0	0	0
Cardiopulmonary failure	0	1 (0.7)	0	0	0	0
Cerebral infarction	0	1 (0.7)	0	0	0	0
Circulatory collapse	0	1 (0.7)	0	0	0	0
Coronary artery disease	0	1 (0.7)	0	0	0	0
Ischaemic cerebral infarction	1 (0.4)	0	0	0	0	0
Myocardial rupture	0	1 (0.7)	0	0	0	0
Pericardial effusion	0	1 (0.7)	0	1 (0.4)	0	0
Pneumonitis	0	0	1 (2.0)	0	0	0
Urosepsis	0	0	1 (2.0)	0	0	0
Cardiac arrest	0	0	0	0	0	0
Serious adverse events	93 (39.9)	86 (61.9)	32 (65.3)	80 (33.8)	43 (30.9)	24 (46.2)
Pulmonary embolism	9 (3.9)	13 (9.4)	4 (8.2)	5 (2.1)	4 (2.9)	1 (1.9)
Pneumonia	8 (3.4)	7 (5.0)	5 (10.2)	10 (4.2)	8 (5.8)	4 (7.7)
Deep vein thrombosis	7 (3.0)	4 (2.9)	1 (2.0)	1 (0.4)	0	1 (1.9)
Pleural effusion	6 (2.6)	4 (2.9)	0	7 (3.0)	7 (5.0)	3 (5.8)
ALT increased	6 (2.6)	2 (1.4)	0	4 (1.7)	2 (1.4)	0
Infusion related reaction	5 (2.1)	4 (2.9)	0	0	0	0
COVID-19	4 (1.7)	3 (2.2)	3 (6.1)	3 (1.3)	3 (2.2)	3 (5.8)
Rash	4 (1.7)	1 (0.7)	2 (4.1)	0	0	0
Pneumonitis	3 (1.3)	2 (1.4)	3 (6.1)	2 (0.8)	3 (2.2)	3 (5.8)
Hyponatraemia	2 (0.9)	3 (2.2)	0	2 (0.8)	0	2 (3.8)
Interstitial lung disease	2 (0.9)	3 (2.2)	0	3 (1.3)	1 (0.7)	1 (1.9)
Respiratory failure	1 (0.4)	5 (3.6)	0	2 (0.8)	0	0

*Adverse events leading to death occurring in any age group in the Ami/Laz group, Serious adverse events reported by ≥2% of subjects in any age group

Based on the above analysis results (1) (2), Ami/Laz is recommended for patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, regardless of age.

PMDA's view:

Although the reason for a trend towards higher hazard ratios of PFS and OS for Ami/Laz vs. Osi in patients aged ≥65 and <75 years and patients aged ≥75 years than in patients aged <65 years in the MARIPOSA study has not been identified, at least given the following points, the package inserts and other materials for Ami and Laz should advise that whether to use Ami/Laz in patients aged ≥65 years should be decided carefully,

according to individual patients' conditions, and provide the information on the incidence of adverse events by age group in the MARIPOSA study.

- While the incidences of adverse events leading to death, serious adverse events, and adverse events leading to treatment discontinuation tended to be higher in patients aged ≥65 and <75 years than in patients aged <65 years in the Ami/Laz group, a similar trend was not observed in the Osi group.
- Ami/Laz is Ami as an add-on therapy to an EGFR-TKI, i.e., the current standard treatment for *EGFR* mutation-positive unresectable advanced or recurrent NSCLC. The incidences of serious adverse events etc. tended to be higher in the Ami/Laz group than in the Osi and Laz groups also in the overall population of the MARIPOSA study.

7.R.5 Dosage and administration

The applicant proposed the statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami (the present partial change application) and Laz as shown in the table below.

<table>
<tr><th></th><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>Ami*</td><td>
[Patients with EGFR exon 20 insertion mutation-positive disease]
The usual adult dosage of amivantamab (Ami) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.
<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="5">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,400 mg</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>1,750 mg</td></tr>
<tr><td rowspan="5">Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,400 mg</td></tr>
<tr><td>Day 8, Day 15</td><td>1,750 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,750 mg</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>2,100 mg</td></tr>
</table>
[Patients with EGFR mutation-positive disease]
The usual adult dosage of amivantamab (Ami) in combination with Laz is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.
<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="3">Less than 80 kg</td><td rowspan="2">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>700 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 8, Day 15, Day 22</td><td>1,050 mg</td></tr>
<tr><td>Day 1, Day 15</td><td>1,050 mg</td></tr>
<tr><td rowspan="4">Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td></tr>
</table>
</td><td>
● Administer the diluted solution according to the infusion rates in the table below.
[Patients with EGFR exon 20 insertion mutation-positive disease]
Doses and infusion rates of Ami (Ami in combination with carboplatin and pemetrexed sodium)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>33 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>1,750 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,400 mg</td><td>25 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,750 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,750 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,750 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>2,100 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

[Patients with EGFR mutation-positive disease]
Doses and infusion rates of Ami (Ami in combination with Laz)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 8</td><td>1,050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 15, Day 22</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="5">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 22</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

● Prior to the initial infusion of Ami (Cycle 1, Day 1 and Day 2), glucocorticoids, antihistamines, and antipyretics should be administered, and H_2 receptor antagonists and antiemetics should also be administered as needed to reduce the risk of infusion reactions. For subsequent infusions from Cycle 1 Day 8 onwards, antihistamines and antipyretics should be administered, and glucocorticoids, H_2 receptor antagonists, and antiemetics should also be administered as needed.
● Since Ami in combination with Laz can cause venous thromboembolism, apixaban 2.5 mg BID taken orally or edoxaban 30 mg QD taken orally is recommended for the first 4 months of treatment.
● Recommended Ami dosage modifications for adverse reactions
</td></tr>
<tr><td>Laz</td><td>The usual adult dosage is 240 mg of Laz orally once daily administered in combination with Ami. The dosage should be reduced, as appropriate, according to the patient's condition.</td><td>
● The efficacy and safety of Laz monotherapy have not been established.
● Since Laz in combination with Ami can cause venous thromboembolism, apixaban 2.5 mg BID taken orally or edoxaban 30 mg QD taken orally is recommended for the first 4 months of treatment.
● Recommended Laz dosage modifications for adverse reactions
</td></tr>
</table>

*Underline denotes additions to the approved labeling.

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following considerations, PMDA concluded that the statements in the table below should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz.

<table>
<tr><th></th><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>Ami*</td><td>
[EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC]
The usual adult dosage of amivantamab (Ami) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.
<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="5">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
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<tr><td rowspan="4">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>700 mg</td></tr>
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</td><td>
● Administer the diluted solution according to the infusion rates in the table below.
Doses and infusion rates of Ami (Ami in combination with carboplatin and pemetrexed sodium)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>33 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>1,750 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,400 mg</td><td>25 mL/h</td><td>50 mL/h</td></tr>
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Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

Doses and infusion rates of Ami (Ami in combination with Laz)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
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<tr><td>Day 2</td><td>1,050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 22</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

● Prior to the initial infusion of Ami (Cycle 1, Day 1 and Day 2), glucocorticoids, antihistamines, and antipyretics should be administered, and H_2 receptor antagonists and antiemetics should also be administered as needed to reduce the risk of infusion reactions. For subsequent infusions from Cycle 1 Day 8 onwards, antihistamines and antipyretics should be administered, and glucocorticoids, H_2 receptor antagonists, and antiemetics should also be administered as needed.
● When administering Ami in combination with Laz, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.
● Recommended Ami dosage modifications for adverse reactions
</td></tr>
<tr><td>Laz</td><td>The usual adult dosage is 240 mg of Laz orally once daily administered in combination with Ami. The dosage should be reduced, as appropriate, according to the patient's condition.</td><td>
● When administering Laz in combination with Ami, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.
● Recommended Laz dosage modifications for adverse reactions
</td></tr>
</table>

*Underline denotes additions to the approved labeling.

7.R.5.1 Dosage and administration for Ami and Laz

The applicant's explanation about the dosing rationale for Ami and Laz:

Taking account of the points in the table below, the dosing regimens were selected for the Ami/Laz cohort of Study EDI1001 and Japanese phase Ib part of Study NSC1001, which demonstrated the tolerability of Ami/Laz. The MARIPOSA study with the same dosing regimens as in this cohort was conducted. Since the study demonstrated the efficacy and clinical usefulness of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC [see Sections 7.R.2 and 7.R.3], the dosing regimens of Ami and Laz and the precautionary statement regarding the infusion rate of Ami in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section were proposed based on this study.

Ami	● In the Ami monotherapy cohorts of Study EDI1001, the RP2D regimen of Ami monotherapy using a 4-week cycle was 1,050 mg for patients weighing <80 kg or 1,400 mg for patients weighing ≥80 kg administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles (The first dose in Cycle 1 was split over 2 days [350 mg on Cycle 1 Day 1 and the remainder on Cycle 1 Day 2]) (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024"). ● Given that the majority of infusion reactions on Cycle 1 Day 1 occurred within 2 hours of infusion in the Ami monotherapy cohorts of Study EDI1001, the infusion rate was to be increased after 2 hours in the absence of infusion reactions on Cycle 1 Days 1 and 2. From Cycle 1 Day 8 onwards, the infusion rate was to be escalated with each infusion to the maximum rate in Cycle 2.
Laz	● In Japanese phase I part of Study NSC1001, the RP2D of Laz monotherapy was 240 mg QD orally.

Since the same premedication instructions for infusion reactions with Ami as in the clinical study of Ami in the currently approved indication were used in the MARIPOSA study, the same statement in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section as that for the currently approved indication was proposed for Ami. Since there are no data from clinical studies that evaluated the efficacy and safety of Laz monotherapy, "the efficacy and safety of Laz monotherapy have not been established" was included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section for Laz.

Based on the above, the statements in the table below were included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz.

<table>
<tr><th></th><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>Ami*</td><td>[Patients with EGFR exon 20 insertion mutation-positive disease]
Omitted [see Section 7.R.5]

[Patients with EGFR mutation-positive disease]
The usual adult dosage of amivantamab (Ami) in combination with Laz is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="5">Less than 80 kg
Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>700 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,050 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td></tr>
</table>
</td><td>● Administer the diluted solution according to the infusion rates in the table below.
[Patients with EGFR exon 20 insertion mutation-positive disease]
Doses and infusion rates of Ami (Ami in combination with carboplatin and pemetrexed sodium)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Omitted [see Section 7.R.5]</td></tr>
</table>

[Patients with EGFR mutation-positive disease]
Doses and infusion rates of Ami (Ami in combination with Laz)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 8</td><td>1,050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 15, Day 22</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="5">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 22</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

● Premedications to reduce the risk of infusion reactions with Ami</td></tr>
<tr><td>Laz</td><td>The usual adult dosage is 240 mg of Laz orally once daily administered in combination with Ami. The dosage should be reduced, as appropriate, according to the patient's condition.</td><td>● The efficacy and safety of Laz monotherapy have not been established.</td></tr>
</table>

*Underline denotes additions to the approved labeling.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, since the DOSAGE AND ADMINISTRATION section for Laz specifies that Laz is administered in combination with Ami, there is no need to include "the efficacy and safety of Laz monotherapy have not been established" in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section for Laz.

Based on the above, the statements in the table below should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz.

<table>
<tr><th></th><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>Ami*</td><td>[EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC]
Omitted [see Section 7.R.5]

[EGFR mutation-positive unresectable advanced or recurrent NSCLC]
The usual adult dosage of amivantamab (Ami) in combination with Laz is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="4">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>700 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,050 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td></tr>
<tr><td rowspan="4">Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td></tr>
</table>
</td><td>● Administer the diluted solution according to the infusion rates in the table below.
Doses and infusion rates of Ami (Ami in combination with carboplatin and pemetrexed sodium)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Omitted [see Section 7.R.5]</td></tr>
</table>
Doses and infusion rates of Ami (Ami in combination with Laz)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 8</td><td>1,050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 15, Day 22</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="5">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 22</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

● Premedications to reduce the risk of infusion reactions with Ami</td></tr>
<tr><td>Laz</td><td>The usual adult dosage is 240 mg of Laz orally once daily administered in combination with Ami. The dosage should be reduced, as appropriate, according to the patient's condition.</td><td>－</td></tr>
</table>

* Underline denotes additions to the approved labeling. －, Not applicable

7.R.5.2 Use of prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz

The applicant's explanation about the need for the use of prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz:

At the time of recommending prophylactic anticoagulation to prevent venous thromboembolism, patient enrollment in the MARIPOSA study was complete, and the limited number of patients received prophylactic anticoagulation at the time of initiation of treatment with Ami/Laz [see Section 7.R.3.4]. On the other hand, the same dosing regimens as in the Ami/Laz group of the MARIPOSA study were used in a global phase III study to evaluate the PK etc. of Laz with subcutaneous Ami compared with intravenous Ami in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously treated with chemotherapy (PALOMA-3 study). At the time of initiation of the PALOMA-3 study, the above prophylactic anticoagulation was recommended for the first 4 months of treatment with Ami/Laz. Concerning the PALOMA-3 study, the results from patients treated with Laz + intravenous Ami are described below.

Table 73 and Table 74 show the incidences of venous thromboembolism and bleeding,[81] respectively, in the following patients: 171 patients who received prophylactic anticoagulant therapy[82] at the time of study treatment initiation among 210 patients in the safety analysis set for the Ami/Laz group of the PALOMA-3 study and 421 patients in the overall Ami/Laz group of the MARIPOSA study.

Table 73. Incidence of venous thromboembolism
(Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

	n (%)			
	Overall population		Japanese subgroup	
PT (MedDRA ver.25.0)	Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 171	Overall Ami/Laz group of the MARIPOSA study N = 421	Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 9	Overall Ami/Laz group of the MARIPOSA study N = 29
Venous thromboembolism of any grade	20 (11.7)	157 (37.3)	1 (11.1)	11 (37.9)
Grade ≥3 venous thromboembolism	2 (1.2)	47 (11.2)	0	5 (17.2)
Venous thromboembolism leading to death	0	2 (0.5)	0	0
Serious venous thromboembolism	3 (1.8)	46 (10.9)	0	5 (17.2)
Venous thromboembolism leading to study drug discontinuation	0	12 (2.9)	0	3 (10.3)

Table 74. Incidence of bleeding
(Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

	n (%)			
	Overall population		Japanese subgroup	
PT (MedDRA ver.25.0)	Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 171	Overall Ami/Laz group of the MARIPOSA study N = 421	Patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 9	Overall Ami/Laz group of the MARIPOSA study N = 29
Bleeding of any grade	48 (28.1)	116 (27.6)	4 (44.4)	10 (34.5)
Grade ≥3 bleeding	1 (0.6)	6 (1.4)	0	0
Bleeding leading to death	0	1 (0.2)	0	0
Serious bleeding	2 (1.2)	7 (1.7)	0	0
Bleeding leading to study drug discontinuation	0	1 (0.2)	0	0

Although there are limitations to cross-study comparisons, (i) the incidence of venous thromboembolism was lower in (1) patients who received prophylactic anticoagulant therapy at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study than in (2) the Ami/Laz group of the MARIPOSA study in which the limited number of patients received prophylactic anticoagulant therapy at the time of study treatment

[81] Events in the MedDRA SMQ "haemorrhages (narrow)" and events coded to MedDRA PTs "tumour haemorrhage," "haematuria," "conjunctival haemorrhage," "haematochezia," "haemoptysis," "pulmonary haemorrhage," "gingival bleeding," "cerebral haemorrhage," "epistaxis," "haemorrhagic stroke," "subdural haemorrhage," "anal haemorrhage," "haemorrhoidal haemorrhage," "haemorrhage," "vaginal haemorrhage," "gastrointestinal haemorrhage," "intra-abdominal haemorrhage," "skin haemorrhage," "eye haemorrhage," "pulmonary alveolar haemorrhage," "ear haemorrhage," "tongue haemorrhage," "haemothorax," "upper gastrointestinal haemorrhage," "rectal haemorrhage," "vulval haemorrhage," "haemorrhage subcutaneous," "mouth haemorrhage," "iris haemorrhage," and "laryngeal haemorrhage" were counted.

[82] Anticoagulants administered to ≥3 subjects (some subjects received more than one type of anticoagulant) were rivaroxaban (76 subjects [36.2%]), apixaban (54 subjects [25.7%]), enoxaparin sodium (35 subjects [16.7%]), edoxaban (17 subjects [8.1%]), and fondaparinux sodium and bemiparin sodium (unapproved in Japan) (3 subjects [1.4%]).

initiation, and (ii) there were no clear differences in the incidence of bleeding between the above patients (1) and (2). In addition, foreign clinical practice guidelines [NCCN guidelines (NSCLC) (v.10.2024)] etc. recommend prophylactic anticoagulation at the time of initiation of Ami/Laz treatment to prevent venous thromboembolism. Given these points, prophylactic anticoagulation is recommended for the first 4 months of treatment with Ami/Laz to prevent venous thromboembolism.

PMDA asked the applicant to explain the choice and dosing regimen of prophylactic anticoagulants to prevent venous thromboembolism associated with Ami/Laz.

The applicant's response:
In Japan, there are no drugs approved for the indication of the prevention of venous thromboembolism associated with anti-cancer agents, and the Japanese clinical practice guideline etc. include no recommendations for prophylactic anticoagulants to prevent venous thromboembolism associated with anti-cancer agents. On the other hand, foreign clinical practice guidelines[83)] recommend prophylaxis with oral apixaban 2.5 mg BID as an option for patients with solid tumors at increased risk of venous thromboembolism,[84)] receiving systemic anti-cancer therapy, based on the results of a foreign clinical study to assess the efficacy and safety of prophylaxis with apixaban for venous thromboembolism in patients with cancer as shown in the table below.

Study ID (Published article)	Study design	Dosing regimen	Study population	Results
AVERT study (*N Engl J Med*. 2019; 380: 711-9)	A randomized, double-blind, phase II study	Apixaban 2.5 mg BID or placebo administered for 180 days	Ambulatory patients with cancer who were initiating chemotherapy and had a Khorana score of ≥2	[Efficacy] The incidences of venous thromboembolism (proximal deep vein thrombosis or pulmonary embolism) within the first 180 days after randomization were 4.2% (12 of 288 patients) in the apixaban group and 10.2% (28 of 275 patients) in the placebo group, and apixaban therapy resulted in a statistically significantly lower rate of venous thromboembolism (hazard ratio [95% CI], 0.41 [0.26, 0.65]). [Safety] The incidences of major bleeding were 3.5% (10 patients) in the apixaban group and 1.8% (5 patients) in the placebo group.

Given the above situation and the following points etc., the package insert should advise that oral apixaban 2.5 mg BID should be administered as a prophylactic anticoagulant to prevent venous thromboembolism associated with Ami/Laz in Japanese patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC.

- Although there are limitations to cross-study comparisons, (i) the incidence of venous thromboembolism was lower in (1) patients who received apixaban at the time of study treatment initiation in the safety analysis set for the Ami/Laz group of the PALOMA-3 study than in (2) the Ami/Laz group of the

83) NCCN guidelines (Cancer-Associated Venous Thromboembolic Disease) (v.2.2024) and ASCO guidelines (2023)
84) Patients with a Khorana score (*Blood.* 2008; 111: 4902-7) of ≥2
Khorana score consists of the following 5 variables:
- Primary site of cancer
  - △ stomach, pancreas: 2 points
  - △ lung, lymphoma, gynecologic, bladder, testicular: 1 point
- Pre-chemotherapy platelet count ≥350×10^9/L: 1 point
- Hemoglobin <10 g/dL, or use of red blood cell growth factors: 1 point
- Pre-chemotherapy leukocyte count >11×10^9/L: 1 point
- BMI ≥35 kg/m^2: 1 point

MARIPOSA study in which the limited number of patients received prophylactic anticoagulant therapy at the time of study treatment initiation, and (ii) there were no clear differences in the incidence of bleeding between the above patients (1) and (2) [see Table 75 and Table 76].

- In the Ami/Laz group of the PALOMA-3 study, a dosing regimen of apixaban 2.5 mg BID was mainly used.[85)]

Table 75. Incidence of venous thromboembolism
(Patients who received apixaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

PT (MedDRA ver.25.0)	n (%)	
	Overall population	
	Patients who received apixaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 54	Overall Ami/Laz group of the MARIPOSA study N = 421
Venous thromboembolism of any grade	4 (7.4)	157 (37.3)
Grade ≥3 venous thromboembolism	0	47 (11.2)
Venous thromboembolism leading to death	0	2 (0.5)
Serious venous thromboembolism	0	46 (10.9)
Venous thromboembolism leading to study drug discontinuation	0	12 (2.9)

Table 76. Incidence of bleeding
(Patients who received apixaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

PT (MedDRA ver.25.0)	n (%)	
	Overall population	
	Patients who received apixaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 54	Overall Ami/Laz group of the MARIPOSA study N = 421
Bleeding of any grade	14 (25.9)	116 (27.6)
Grade ≥3 bleeding	0	6 (1.4)
Bleeding leading to death	0	1 (0.2)
Serious bleeding	0	7 (1.7)
Bleeding leading to study drug discontinuation	0	1 (0.2)

- There were no clear differences in the PK of apixaban in the currently approved indications between Japanese and non-Japanese populations, and the dosing regimens of apixaban for the treatment of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) and for the reduction in the risk of recurrent venous thromboembolism are the same between Japan and overseas.
- Given the following points, clinically relevant pharmacokinetic interactions between apixaban and Ami or Laz are unlikely to occur.
  - Though apixaban is a substrate of CYP3A, P-gp, and BCRP *in vitro*, no precautionary statements about coadministration with weak CYP3A inhibitors or BCRP inhibitors are included in the package insert (see "Package insert for Eliquis tablets 2.5 mg and 5 mg as of July 17, 2024").
  - Although Laz inhibited CYP3A, P-gp, and BCRP *in vitro*, Laz is considered to have a weak inhibitor effect on CYP3A, and Laz is unlikely to cause pharmacokinetic interactions vis inhibition of P-gp in clinical use (see Sections 4.2.5.1, 4.2.5.3, and 6.2.2.3 and "Drug interaction guideline for drug

[85)] Among 54 patients who received apixaban, 2.5 mg BID was used in 36 patients, 5 mg BID was used in 10 patients, 2.5 mg QD was used in 4 patients, 5 mg QD was used in 2 patients, 10 mg BID was used in 1 patient, and 10 mg QD was used in 1 patient.

development and labeling recommendations" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018).

- While CYP3A is mainly involved in the oxidative metabolism of Laz, and GST M1-1 is mainly involved in the glutathione conjugation of Laz, apixaban does not inhibit or induce CYP3A, and its effect on GST has not been reported (see Section 4.2.3.1 and "Summary of the product application for Eliquis tablets 2.5 mg and 5 mg as of December 21, 2011").
- Ami is an antibody drug and is expected to be catabolized into small peptides and amino acids and cleared (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024").

- A certain amount of apixaban safety information from Japanese patients for the currently approved indications is available (see "Re-examination Report on Eliquis tablets 2.5 mg and 5 mg as of May 17, 2022"), and a dose of apixaban 2.5 mg is lower as compared with the dosing regimens for the currently approved indications.

In addition, given the following points etc., oral edoxaban 30 mg QD can also be used as a prophylactic anticoagulant to prevent venous thromboembolism associated with Ami/Laz.

- The results from post-marketing surveillance and specified clinical studies of oral edoxaban 30 mg QD in patients with cancer with venous thromboembolism, etc. (*Circ Rep*. 2020; 2: 192-202, *BMC Cancer*. 2022; 22: 1322, *Circulation*. 2023; 148: 1665-76) are available.
- Although there are limitations to cross-study comparisons, (i) the incidence of venous thromboembolism was lower in (1) patients who received edoxaban at the time of study treatment initiation in the safety analysis set for the Ami/Laz group of the PALOMA-3 study than in (2) the Ami/Laz group of the MARIPOSA study in which the limited number of patients received prophylactic anticoagulant therapy at the time of study treatment initiation, and (ii) no serious bleeding etc. were reported in the above patients (1) [see Table 77 and Table 78].
- In the Ami/Laz group of the PALOMA-3 study, a dosing regimen of edoxaban 30 mg QD was mainly used.[86)]

Table 77. Incidence of venous thromboembolism
(Patients who received edoxaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

PT (MedDRA ver.25.0)	n (%)	
	Overall population	
	Patients who received edoxaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 17	Overall Ami/Laz group of the MARIPOSA study N = 421
Venous thromboembolism of any grade	2 (11.8)	157 (37.3)
Grade ≥3 venous thromboembolism	0	47 (11.2)
Venous thromboembolism leading to death	0	2 (0.5)
Serious venous thromboembolism	0	46 (10.9)
Venous thromboembolism leading to study drug discontinuation	0	12 (2.9)

[86)] Among 17 patients who received edoxaban, 30 mg QD was used in 12 patients, 60 mg QD was used in 4 patients, and 30 mg BID was used in 1 patient.

Table 78. Incidence of bleeding
(Patients who received edoxaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study, data cutoff date of January 3, 2024; The overall Ami/Laz group of the MARIPOSA study, data cutoff date of August 11, 2023; Safety analysis set)

PT (MedDRA ver.25.0)	n (%)	
	Overall population	
	Patients who received edoxaban at the time of study treatment initiation in the Ami/Laz group of the PALOMA-3 study N = 17	Overall Ami/Laz group of the MARIPOSA study N = 421
Bleeding of any grade	8 (47.1)	116 (27.6)
Grade ≥3 bleeding	0	6 (1.4)
Bleeding leading to death	0	1 (0.2)
Serious bleeding	0	7 (1.7)
Bleeding leading to study drug discontinuation	0	1 (0.2)

- In the Ami/Laz group of the PALOMA-3 study, edoxaban was used in 8 of 9 Japanese patients who received prophylactic anticoagulant therapy at the time of study treatment initiation.
- Clinically relevant pharmacokinetic interactions between edoxaban and Ami or Laz are unlikely to occur.
- A certain amount of safety information from Japanese patients for the currently approved indications is available (see "Re-examination Report on Lixiana Tablets 15 mg, 30 mg, and 60 mg and Lixiana OD Tablets 15 mg, 30 mg, and 60 mg as of July 15, 2022), and the dosing regimen is the same as that for the prevention of venous thromboembolism in patients undergoing lower-limb orthopedic surgery in Japan.

Based on the above, the statements in the table below were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz. The dosing regimens of apixaban and edoxaban are presented in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz, in accordance with "Handling of marketing applications etc. for drugs, medical devices, and regenerative medical products to be combined with other drugs" (PSB/PED Notification No. 0531-1, PSB/MDED Notification No.0531-3, and PSB/PSD Notification No. 0531-1, dated May 31, 2024).

Ami	Since Ami in combination with Laz can cause venous thromboembolism, apixaban 2.5 mg BID taken orally or edoxaban 30 mg QD taken orally is recommended for the first 4 months of treatment.
Laz	Since Laz in combination with Ami can cause venous thromboembolism, apixaban 2.5 mg BID taken orally or edoxaban 30 mg QD taken orally is recommended for the first 4 months of treatment.

PMDA's view:

PMDA accepted the above explanation about apixaban by the applicant, and concluded that it is acceptable to advise that oral apixaban 2.5 mg BID should be administered as a concomitant medication to prevent venous thromboembolism associated with Ami/Laz. On the other hand, there are no data from clinical studies intended to assess the efficacy and safety of edoxaban for the prevention of venous thromboembolism in patients with cancer, and Japanese and foreign clinical practice guidelines include no recommendations for edoxaban. Given these points etc., it is unacceptable at present to advise that edoxaban should be administered as a concomitant medication to prevent venous thromboembolism associated with Ami/Laz.

Based on the above, the statements in the table below should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz.

Ami	When administering Ami in combination with Laz, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.
Laz	When administering Laz in combination with Ami, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.

The number of Japanese patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC who received apixaban for the prevention of venous thromboembolism associated with Ami/Laz is limited. Thus, post-marketing information on the incidences of venous thromboembolism and bleeding in Japanese patients who received apixaban to prevent venous thromboembolism associated with Ami/Laz should be collected, and if new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

7.R.5.3 Recommended dosage modifications

The applicant's explanation about the recommended dosage modifications for Ami and Laz:

The MARIPOSA study was conducted according to the Ami and Laz dosage modification guidelines for adverse events, and the study demonstrated the clinical usefulness of Ami/Laz. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections included a revised version of these guidelines as shown below.

Venous thromboembolism	In the MARIPOSA study, in the event of recurrent venous thromboembolism during therapeutic anticoagulation for venous thromboembolism associated with Ami/Laz, Ami/Laz was to be discontinued, whereas treatment could also continue with either Ami or Laz at the discretion of the physician. However, given that the current standard treatment for the patient population of the MARIPOSA study is EGFR-TKIs, and that the information on the efficacy and safety of Ami monotherapy is limited, etc., the revised version should state that Ami should be permanently discontinued, and treatment can continue with Laz.
Grade 2 skin or nail reactions	In the MARIPOSA study, in the event of Grade 2 skin or nail reaction, dose reduction of Ami or Laz[87)] was to be considered, and the patient was to be reassessed every 2 weeks. Revised version ● Since whether to continue at the same dose or reduce the dose was left to the judgement of the investigator in the MARIPOSA study, if there is no improvement at reassessment after 2 weeks (instead of at the time of Grade 2 skin or nail reaction), the dose of Ami should be reduced. ● Given that the current standard treatment for the patient population of the MARIPOSA study is EGFR-TKIs, and that the information on the efficacy and safety of Ami monotherapy is limited, etc., if the dose is reduced, preferentially reduce the dose of Ami first, and then if there is no improvement, reduce the dose of Laz until recovery to Grade ≤1.
Grade 3 skin or nail reactions	In the MARIPOSA study, in the event of Grade 3 skin or nail reaction, Ami and Laz were to be withheld, and based on once weekly reassessment and discussion with medical monitor, Ami and Laz were to be resumed at the dose at which the reaction occurred or at a reduced dose.[87)] Revised version ● As in the case of Grade 2 skin or nail reaction, preferentially reduce the dose of Ami first, if the dose is reduced. ● Although the implementation of once weekly reassessment in the MARIPOSA study is unknown, as the event could be managed ultimately at the discretion of the investigator in the MARIPOSA study, once weekly reassessment is omitted. ● Based on the results of previous clinical studies, conservative guidance is provided: If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Ami and Laz.
Grade 2 other* adverse reactions	In the MARIPOSA study, in the event of Grade 2 other adverse reactions, treatment was to be continued or dose interruption or reduction of Ami or Laz was to be considered.[87)] Treatment was to be resumed at the dose at which the reaction occurred or at a reduced dose for interruptions of <28 days. However, the management of adverse events is different according to the nature of adverse events, etc., recommended dosage modifications for Grade 2 other adverse reactions are omitted.
Grade 3 or 4 other* adverse reactions	Guidance on permanent discontinuation of Ami and Laz in the event of Grade 3 or 4 other adverse reactions was not provided in the MARIPOSA study. However, conservative guidance is provided: If recovery does not occur within 28 days, permanent discontinuation of Ami and Laz should be considered.

*Other than infusion reactions, ILD, venous thromboembolism (Ami/Laz), and skin or nail reactions

[87)] If the reported adverse reaction was strongly suspected to be related to Laz, dose reduction of Laz was to be considered.

PMDA's view:

Except for the points in the table below, PMDA largely accepted the above explanation by the applicant.

Overall (Ami and Laz)	Recommended dosage modifications for Ami should be included in the Ami package insert, and recommended dosage modifications for Laz should be included in the Laz package insert.
Venous thromboembolism (Ami and Laz)	In the MARIPOSA study, in the event of recurrent venous thromboembolism during therapeutic anticoagulation for venous thromboembolism associated with Ami/Laz, Ami and Laz were to be discontinued. Given this point, the revised version should state as follows: If the above event occurs, not only Ami but also Laz should be permanently discontinued, but treatment can continue with Laz at the same dose level at the discretion of the physician.
Grade 1 skin or nail reactions (Ami and Laz)	In the MARIPOSA study, in the event of Grade 1 skin or nail reaction, the patient was to be reassessed after 2 weeks. However, since patients are required to visit at least every 2 weeks to receive Ami for treatment with Ami/Laz, and Laz dosage modifications were made based on the above reassessment in the limited number of patients in the Ami/Laz group of the MARIPOSA study, there is little need for this guidance as recommended dosage modifications.
Grade 2 skin or nail reactions (Ami and Laz)	Given that a certain number of patients had Grade 2 skin or nail reactions leading to dose reduction of Ami or Laz in the MARIPOSA study, based on the guidance used in the MARIPOSA study, the revised version should state that if the above event occurs during treatment with Ami/Laz, dose reduction of Ami or Laz should be considered.
Grade 3 skin or nail reactions (Ami and Laz)	Given that the implementation of once weekly reassessment in patients with Grade 3 skin or nail reactions in the MARIPOSA study is unknown, based on the guidance used in the MARIPOSA study, the revised version should state as follows: If the above event occurs during treatment with Ami/Laz, Ami and Laz should be withheld, and the patient should be monitored once weekly. Given that a certain number of patients had Grade 3 skin or nail reactions leading to dose reduction of either Ami or Laz or both in the MARIPOSA study, the revised version should state that dose reduction should be considered, and then treatment should be resumed.
Grade 4 skin or nail reactions and severe bullous, blistering or exfoliating skin conditions (Ami and Laz)	Guidance on once weekly reassessment in the event of Grade 4 or severe skin or nail reaction was not provided in the MARIPOSA study. Ami was to be permanently discontinued, and Laz was to be withheld, and upon recovery to Grade ≤2, Laz was to be resumed at the same dose or at a reduced dose. However, given the following points, similar guidance as in the case of Grade 3 skin or nail reactions should be provided for Grade 4 skin or nail reactions. ● In the Ami/Laz and Laz groups of the MARIPOSA study, though there were no Grade 4 skin or nail reactions, a certain number of patients had Grade 3 skin or nail reactions leading to dose reduction of either Ami or Laz or both. ● In the event of Grade 4 skin or nail reaction associated with Ami/Laz, Ami will be permanently discontinued. ● In the Laz group of the MARIPOSA study, there were no skin disorders leading to death or serious skin disorders. Although no severe bullous, blistering or exfoliating skin conditions were reported in the Ami/Laz or Laz group of the MARIPOSA study, considering their seriousness, if those events occur, Laz should also be permanently discontinued.
Grade 2 other* adverse reactions (Ami and Laz)	In the MARIPOSA study, Grade 2 other adverse reactions led to dose interruption or reduction of Ami or Laz, or Ami or Laz was withheld for <28 days and resumed at a reduced dose due to Grade 2 other adverse reactions in a certain number of patients. Given these findings, similar guidance as in the MARIPOSA study should be provided.
Grade 4 other* adverse reactions (Laz)	In the MARIPOSA study, a certain number of patients had Grade 4 other adverse reactions leading to discontinuation of Laz, and Grade 4 other adverse reactions for which Laz was withheld and resumed were mainly laboratory abnormalities. Given these findings, the revised version should state that if the above events occur, treatment should be permanently discontinued as a rule, and then the criteria for resuming treatment after interruption should be provided.

*Other than infusion reactions, ILD, venous thromboembolism (Ami/Laz), and skin or nail reactions

Based on the above, the following guidance should be included as the recommended dosage modifications for Ami and Laz in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

[Ami] (Underline denotes additions to the approved labeling.)

- In the event of adverse reactions to Ami, reduce the dose, interrupt, withhold, or discontinue Ami, as per the tables below.

Ami dose reductions for adverse reactions

Dose at which the adverse reaction occurred	First dose reduction	Second dose reduction	Third dose reduction
1,050 mg	700 mg	350 mg	Discontinue Ami
1,400 mg	1,050 mg	700 mg	
1,750 mg	1,400 mg	1,050 mg	
2,100 mg	1,750 mg	1,400 mg	

Recommended Ami dosage modifications for adverse reactions

Infusion Reactions

Severity*	Dosage Modifications
Grade 1 or 2	● Interrupt Ami infusion. ● Upon resolution of symptoms, resume the infusion at 50% of the infusion rate at which the reaction occurred. ● If there are no additional symptoms after 30 minutes, the infusion rate may be increased to 100% of the infusion rate at the time of interruption. In the absence of additional symptoms, the rate may be increased per the recommended infusion rate after 2 hours. ● In the case of second interruption for Grade 2 infusion reaction, consider discontinuation of further treatment on the same day.
Grade 3	● Discontinue further treatment on the same day. ● Decide whether to continue with subsequent dosing according to the patient's condition. Decide the infusion rate according to the patient's condition, based on the guidance for Grade 2 infusion reactions. ● For recurrent Grade 3 infusion reactions, permanently discontinue Ami.
Grade 4	Permanently discontinue Ami.

ILD

Diagnosis	Dosage Modifications
Suspected	Withhold Ami.
Confirmed	Permanently discontinue Ami.

Venous thromboembolism (Ami in combination with Laz)

Situation	Dosage modifications
Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withold Ami until the patient is clinically stable.
Recurrent venous thromboembolism despite therapeutic level anticoagulation	Permanently discontinue Ami.

Skin or nail reactions

Severity*	Dosage Modifications
Grade 1	If there is no improvement after 2 weeks, consider dose reduction.
Grade 2	● When Ami is used in combination with Laz, consider dose reduction. ● If there is no improvement after 2 weeks, consider dose reduction.
Grade 3	● Withhold Ami until recovery to Grade ≤2, and resume Ami at a reduced dose. ● When Ami is used in combination with Laz, withhold Ami and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction and then resume Ami. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Ami.
Grade 4	Permanently discontinue Ami.
Severe bullous, blistering or exfoliating skin conditions	

Other adverse reactions

Severity*	Dosage Modifications
Grade 2	● Consider dose interruption. Consider resuming at a reduced dose if there is improvement after 1 week. ● When Ami is used in combination with Laz, consider dose interruption or dose reduction. Consider resuming at the same dose or at a reduced dose if there is improvement within 28 days. Consider resuming at a reduced dose if there is improvement after 28 days.
Grade 3	● Withhold Ami until recovery to Grade ≤1 or baseline. ● Resume at the same dose if recovery occurs within 1 week. ● Resume at a reduced dose if recovery occurs after 1 week but within 4 weeks. ● Consider permanent discontinuation of Ami if recovery does not occur within 4 weeks.
Grade 4	Permanently discontinue as a rule.

* Severity grade based on NCI-CTCAE v5.0

[Laz]

- In the event of adverse reactions to Laz, reduce the dose, or withhold or discontinue Laz, as per the tables below.

Laz dose reductions for adverse reactions

Dose reduction	First dose reduction	Second dose reduction	Third dose reduction
Dose	160 mg/day	80 mg/day	Discontinue Laz

Recommended dosage modifications for adverse reactions

ILD

Diagnosis	Dosage Modifications
Suspected	Withhold Laz.
Confirmed	Permanently discontinue Laz.

Venous thromboembolism (Laz in combination with Ami)

Situation	Dosage Modifications
Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withhold Laz until the patient is clinically stable.
Recurrent venous thromboembolism despite therapeutic level anticoagulation	Permanently discontinue Laz. Treatment can continue with Laz at the same dose level at the discretion of the physician.

Skin or nail reactions

Severity[*1]	Dosage Modifications
Grade 2	● Consider dose reduction.[*2] ● Monitor the patient after 2 weeks.
Grade 3	Withhold Laz and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction[*2] and then resume Laz. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Laz.
Grade 4	Withhold Laz and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction and then resume Laz. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Laz.
Severe bullous, blistering or exfoliating skin conditions	Permanently discontinue Laz.

Other adverse reactions

Severity[*1]	Dosage Modifications
Grade 2	● Consider dose interruption or dose reduction. ● Consider resuming at the same dose or at a reduced dose if there is improvement within 28 days. Consider resuming at a reduced dose if there is improvement after 28 days.
Grade 3	● Withhold Laz until recovery to Grade ≤1 or baseline. ● Consider resuming at a reduced dose[*3] if recovery occurs within 4 weeks. Consider permanent discontinuation of Laz if recovery does not occur within 4 weeks.
Grade 4	● Permanently discontinue as a rule. ● If Laz is not permanently discontinued, withhold Laz until recovery to Grade ≤1 or baseline. Resume at a reduced dose [*3] if recovery occurs within 4 weeks. Permanently discontinue Laz if recovery does not occur within 4 weeks.

*1 Severity grade based on NCI-CTCAE v5.0
*2 Preferentially reduce the dose of Ami first unless the adverse reaction is strongly suspected to be related to Laz.
*3 Resume Laz and then resume Ami at a reduced dose unless the adverse reaction is strongly suspected to be related to Laz.

7.R.6 RMP (draft)

The Risk Management Plans (RMPs) for Ami and Laz are developed in accordance with "Risk Management Plan Guidance" (PFSB/SD Notification No.0411-1 and PFSB/ELD Notification No.0411-2 dated April 11, 2012) and "Risk Management Plan templates, instructions and publication" (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1 dated March 18, 2022).

Based on the considerations in Section "7.R.3 Safety" etc., PMDA concluded that the RMPs (draft) for Ami and Laz should include the safety specifications presented in Table 79 and Table 80, respectively.

Table 79. Safety and efficacy specifications in the RMP (draft) for Ami

Safety specification		
Important identified risks	Important potential risks	Important missing information
● Infusion reactions ● ILD ● Severe skin disorders ● Venous thromboembolism (Ami in combination with Laz)	● Venous thromboembolism (excluding Ami in combination with Laz) ● Arterial thromboembolism (Ami in combination with Laz) ● Fluid retention ● Severe diarrhoea ● Embryo-fetal toxicity	None
Efficacy specification		
None		

Underline denotes additions in the present partial change application.

Table 80. Safety and efficacy specifications in the RMP (draft) for Laz

Safety specification		
Important identified risks	Important potential risks	Important missing information
● ILD ● Venous thromboembolism (Laz in combination with Ami) ● Hepatic dysfunction ● Severe diarrhoea ● Severe skin disorders ● Cardiac failure	● Venous thromboembolism (excluding Laz in combination with Ami) ● Arterial thromboembolism (Laz in combination with Ami) ● Corneal disorders ● Use in patients with severe hepatic impairment ● Embryo-fetal toxicity	None
Efficacy specification		
None		

7.R.7 Post-marketing investigations

The applicant's explanation about a post-marketing surveillance plan for the present application:

Attention should be paid to the possible occurrence of venous thromboembolism following administration of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC [see Section 7.R.3.4], and prophylactic anticoagulation is recommended to prevent venous thromboembolism associated with Ami/Laz [see Section 7.R.5.2]. However, given that the limited number of patients received prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz in the MARIPOSA study, venous thromboembolism will be included in the safety specification for the surveillance, and post-marketing surveillance is planned to be conducted to investigate the incidence of venous thromboembolism by anticoagulant use, etc., in clinical practice after marketing.

Taking account of the incidence of and time to onset of venous thromboembolism in the MARIPOSA study, the target sample size is 100 patients, and the observation period is 1 year.

PMDA’s view:

Given the following points etc., there is no need to conduct post-marketing surveillance in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, immediately after obtaining approval, on the premise that the implementation of the following measures is ensured through early post-marketing phase vigilance and routine pharmacovigilance practices: provide information on adverse events that require particular attention following administration of Ami/Laz [see Section 7.R.3] to healthcare professionals in clinical practice; collect safety information regarding treatment with Ami/Laz; and take appropriate safety measures based on the currently available information and future information.

- The safety profile of Ami/Laz has been characterized to a certain extent by the data from clinical studies of Ami/Laz.

- With respect to adverse events that require particular attention following administration of Ami/Laz [see Section 7.R.3], there are no clear differences in the nature of adverse events that require attention between Ami/Laz and the existing drugs targeting EGFR (e.g., Ami and Laz) or the existing drugs targeting MET (e.g., Ami).
- There is certain post-marketing clinical experience with the existing EGFR-TKIs.[88)]

However, if a new issue to be investigated is identified after marketing of Ami/Laz, the conduct of post-marketing surveillance etc. as additional pharmacovigilance activities should be considered promptly.

7.3 Adverse events etc. observed in clinical studies

Among clinical study results submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data" and Section "7.2 Reference data." The main adverse events other than deaths are described below.

7.3.1 Global phase I study (Study EDI1001)

7.3.1.1 Part 1 of Ami/Laz cohort

Adverse events and those for which a causal relationship to study drug could not be ruled out occurred in all subjects in the Ami 700/1,050 mg[89)] and Ami 1,050/1,400 mg[90)] groups. Table 81 shows adverse events reported by ≥30% of subjects in either group.

[88)] These EGFR-TKIs have been approved for the following indications.
Osi: "*EGFR* T790M mutation-positive inoperable or recurrent NSCLC resistant to EGFR tyrosine kinase inhibitors" in March 2016, "*EGFR* mutation-positive inoperable or recurrent NSCLC" in August 2018, and "adjuvant therapy in patients with *EGFR* mutation-positive NSCLC" in August 2022
Gefitinib: "inoperable or recurrent NSCLC" in July 2002 and "*EGFR* mutation-positive inoperable or recurrent NSCLC" in November 2011
Erlotinib: "unresectable recurrent or advanced NSCLC after progression following chemotherapy" in October 2007, "unresectable pancreatic cancer" in July 2011," and "*EGFR* mutation-positive unresectable recurrent or advanced NSCLC previously untreated with chemotherapy" in June 2013
Afatinib: "*EGFR* mutation-positive inoperable or recurrent NSCLC" in January 2014
Dacomitinib: "*EGFR* mutation-positive inoperable or recurrent NSCLC" in January 2019

[89)] 700 mg for patients weighing <80 kg, 1,050 mg for patients weighing ≥80 kg

[90)] 1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg

Table 81. Adverse events reported by ≥30% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Ami 700 mg/1,050 mg N = 11		Ami 1,050 mg/1,400 mg N = 52	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	11 (100)	7 (63.6)	52 (100)	27 (51.9)
Skin and subcutaneous tissue disorders				
Dermatitis acneiform	4 (36.4)	0	25 (48.1)	3 (5.8)
Rash	7 (63.6)	1 (9.1)	21 (40.4)	4 (7.7)
Pruritus	4 (36.4)	0	19 (36.5)	0
Metabolism and nutrition disorders				
Hypoalbuminaemia	6 (54.5)	0	37 (71.2)	3 (5.8)
Decreased appetite	4 (36.4)	0	11 (21.2)	0
Infections and infestations				
Paronychia	8 (72.7)	1 (9.1)	42 (80.8)	2 (3.8)
Gastrointestinal disorders				
Stomatitis	5 (45.5)	0	18 (34.6)	0
Investigations				
ALT increased	2 (18.2)	2 (18.2)	27 (51.9)	3 (5.8)
AST increased	2 (18.2)	1 (9.1)	25 (48.1)	2 (3.8)
Nervous system disorders				
Paraesthesia	6 (54.5)	0	14 (26.9)	0
Dizziness	4 (36.4)	0	9 (17.3)	0
Injury, poisoning and procedural complications				
Infusion related reaction	8 (72.7)	1 (9.1)	29 (55.8)	0

Serious adverse events occurred in 5 of 11 subjects (45.5%) in the Ami 700/1,050 mg group and 19 of 52 subjects (36.5%) in the Ami 1,050/1,400 mg group. Those reported by ≥2% of subjects in the Ami 700/1,050 mg group were pleural effusion; dyspnoea; pyrexia; arrhythmia; pneumonia; arthralgia; benign laryngeal neoplasm; and thrombosis (1 subject each [9.1%]). Those reported by ≥2% of subjects in the Ami 1,050/1,400 mg group were pleural effusion; pulmonary embolism; headache; and pericardial effusion (2 subjects each [3.8%]). A causal relationship to study drug could not be ruled out for pulmonary embolism; and headache (2 subjects each) in the Ami 1,050/1,400 mg group.

Adverse events leading to study drug discontinuation occurred in 3 of 11 subjects (27.3%) in the Ami 700/1,050 mg group and 9 of 52 subjects (17.3%) in the Ami 1,050/1,400 mg group. Those reported by ≥2% of subjects in the Ami 700/1,050 mg group were paraesthesia; dyspnoea; and arrhythmia (1 subject each [9.1%]), and there were no adverse events leading to study drug discontinuation reported by ≥2% of subjects in the Ami 1,050/1,400 mg group. A causal relationship to study drug could not be ruled out for paraesthesia (1 subject) in the Ami 700/1,050 mg group.

7.3.1.2 Part 2 of Ami/Laz cohort

Adverse events and those for which a causal relationship to study drug could not be ruled out occurred in all subjects. Table 82 shows adverse events reported by ≥30% of subjects.

Table 82. Adverse events reported by ≥30% of subjects

SOC PT (MedDRA ver.25.0)	n (%) N = 45	
	All Grades	Grade ≥3
Any adverse event	45 (100)	31 (68.9)
Injury, poisoning and procedural complications		
Infusion related reaction	35 (77.8)	0
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	24 (53.3)	2 (4.4)
Dry skin	14 (31.1)	0
Pruritus	14 (31.1)	0
Gastrointestinal disorders		
Nausea	21 (46.7)	0
Constipation	14 (31.1)	0
General disorders and administration site conditions		
Oedema peripheral	17 (37.8)	0
Fatigue	14 (31.1)	0
Infections and infestations		
Paronychia	23 (51.1)	2 (4.4)
Metabolism and nutrition disorders		
Hypoalbuminaemia	18 (40.0)	2 (4.4)
Investigations		
AST increased	17 (37.8)	2 (4.4)
ALT increased	16 (35.6)	6 (13.3)

Serious adverse events occurred in 22 of 45 subjects (48.9%). Those reported by ≥2 subjects were pneumonia (5 subjects [11.1%]); and dyspnoea; pleural effusion; pulmonary embolism; and spinal cord compression (2 subjects each [4.4%]), and a causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in 15 of 45 subjects (33.3%). Those reported by ≥2 subjects were pneumonia (4 subjects [8.9%]), and their causal relationship to study drug was denied.

7.3.2 Global phase I/Ib study (Study NSC1001)

7.3.2.1 Japanese phase I part (Laz monotherapy)

Adverse events occurred in 3 of 3 subjects (100%) in the 160 mg group, 5 of 5 subjects (100%) in the 240 mg group, and 3 of 4 subjects (75.0%) in the 320 mg group, and those for which a causal relationship to study drug could not be ruled out occurred in 3 of 3 subjects (100%) in the 160 mg group, 5 of 5 subjects (100%) in the 240 mg group, and 2 of 4 subjects (50.0%) in the 320 mg group. Table 83 shows adverse events reported by ≥2 subjects in any group.

Table 83. Adverse events reported by ≥2 subjects in any group

SOC PT (MedDRA ver.25.0)	n (%)					
	160 mg N = 3		240 mg N = 5		320 mg N = 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	3 (100)	1 (33.3)	5 (100)	0	3 (75.0)	1 (25.0)
Gastrointestinal disorders						
Diarrhoea	1 (33.3)	0	3 (60.0)	0	2 (50.0)	0
Vomiting	0	0	0	0	2 (50.0)	0
Nervous system disorders						
Peripheral sensory neuropathy	0	0	0	0	2 (50.0)	0
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	0	0	3 (60.0)	0	1 (25.0)	0
Rash	0	0	2 (40.0)	0	1 (25.0)	0
Blood and lymphatic system disorders						
Leukopenia	0	0	2 (40.0)	0	1 (25.0)	0
Investigations						
Blood creatine phosphokinase increased	0	0	2 (40.0)	0	0	0

A serious adverse event occurred in 1 subject (33.3%) (patella fracture) in the 160 mg group. No serious adverse events occurred in the 240 mg group. A serious adverse event occurred in 1 subject (25.0%) (fatigue) in the 320 mg group. A causal relationship to study drug was denied for both events.

There were no adverse events leading to study drug discontinuation.

7.3.2.2 Japanese phase Ib part (Ami + Laz)

Adverse events and those for which a causal relationship to study drug could not be ruled out occurred in all subjects in the Ami 1,050 mg and Ami 1,400 mg cohorts. Table 84 shows adverse events reported by ≥2 subjects in either cohort.

Table 84. Adverse events reported by ≥2 subjects in either cohort

SOC PT (MedDRA ver.25.0)	n (%)			
	Ami 1,050 mg N = 3		Ami 1,400 mg N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	3 (100)	2 (66.7)	3 (100)	3 (100)
Gastrointestinal disorders				
Diarrhoea	1 (33.3)	0	2 (66.7)	0
Constipation	2 (66.7)	0	1 (33.3)	0
Stomatitis	3 (100)	1 (33.3)	1 (33.3)	0
Injury, poisoning and procedural complications				
Infusion related reaction	2 (66.7)	0	3 (100)	0
Metabolism and nutrition disorders				
Hypoalbuminaemia	2 (66.7)	0	3 (100)	2 (66.7)
Skin and subcutaneous tissue disorders				
Dermatitis acneiform	3 (100)	1 (33.3)	2 (66.7)	0
Skin ulcer	1 (33.3)	0	2 (66.7)	0
General disorders and administration site conditions				
Oedema peripheral	1 (33.3)	0	2 (66.7)	0
Investigations				
ALT increased	0	0	2 (66.7)	1 (33.3)
AST increased	0	0	2 (66.7)	0

Serious adverse events occurred in 1 subject (33.3%) in the Ami 1,050 mg cohort and 3 subjects (100%) in the Ami 1,400 mg cohort. The reported serious adverse events were seizure; and dermatitis acneiform (1 subject each [33.3%]) in the Ami 1,050 mg cohort and diverticulitis; cerebral infarction; pleural effusion; and peripheral embolism (1 subject each [33.3%]) in the Ami 1,400 mg cohort. A causal relationship to study drug could not be ruled out for dermatitis acneiform (1 subject) in the Ami 1,050 mg cohort and peripheral embolism (1 subject) in the Ami 1,400 mg cohort.

Adverse events leading to study drug discontinuation occurred in 2 subjects (66.7%) in the Ami 1,050 mg cohort and 2 subjects (66.7%) in the Ami 1,400 mg cohort. The reported adverse events leading to study drug discontinuation were pneumonitis; and stomatitis (1 subject each [33.3%]) in the Ami 1,050 mg cohort and pleural effusion; and peripheral embolism (1 subject each [33.3%]) in the Ami 1,400 mg cohort. A causal relationship to study drug could not be ruled out for pneumonitis; and stomatitis (1 subject each) in the Ami 1,050 mg cohort and peripheral embolism (1 subject) in the Ami 1,400 mg cohort.

7.3.2.3 Ami/Laz cohort A of Global phase Ib part

Adverse events occurred in all subjects, and those for which a causal relationship to study drug could not be ruled out occurred in 161 of 162 subjects (99.4%). Table 85 shows adverse events reported by ≥30% of subjects.

Table 85. Adverse events reported by ≥30% of subjects

SOC PT (MedDRA ver.25.0)	n (%) N = 162	
	All Grades	Grade ≥3
Any adverse event	162 (100)	120 (74.1)
Skin and subcutaneous tissue disorders		
Rash	73 (45.1)	4 (2.5)
Dermatitis acneiform	56 (34.6)	8 (4.9)
Gastrointestinal disorders		
Stomatitis	64 (39.5)	3 (1.9)
Infections and infestations		
Paronychia	84 (51.9)	8 (4.9)
Injury, poisoning and procedural complications		
Infusion related reaction	110 (67.9)	15 (9.3)
Metabolism and nutrition disorders		
Hypoalbuminaemia	76 (46.9)	16 (9.9)
Investigations		
ALT increased	51 (31.5)	6 (3.7)

Serious adverse events occurred in 88 subjects (54.3%). Those reported by ≥2% of subjects were dyspnoea (12 subjects [7.4%]); pneumonia (10 subjects [6.2%]); pneumonitis; general physical health deterioration; and infusion related reaction (6 subjects each [3.7%]); and pleural effusion; and back pain (4 subject each [2.5%]). A causal relationship to study drug could not be ruled out for pneumonitis; and infusion related reaction (6 subjects each); and pneumonia (1 subject).

Adverse events leading to study drug discontinuation occurred in 37 subjects (22.8%). Those reported by ≥2% of subjects were infusion related reaction (7 subjects [4.3%]). A causal relationship to study drug could not be ruled out for infusion related reaction (7 subjects).

7.3.3 Global phase III study (MARIPOSA study)

Adverse events occurred in 421 of 421 subjects (100%) in the Ami/Laz group, 425 of 428 subjects (99.3%) in the Osi group, and 213 of 213 subjects (100%) in the Laz group, and those for which a causal relationship to study drug could not be ruled out occurred in 414 of 421 subjects (98.3%) in the Ami/Laz group, 378 of 428 subjects (88.3%) in the Osi group, and 201 of 213 subjects (94.4%) in the Laz group. Table 86 shows adverse events reported by ≥30% of subjects in any group.

Table 86. Adverse events reported by ≥30% of subjects in any group

SOC PT (MedDRA ver.25.0)	n (%)					
	Ami/Laz N = 421		Osi N = 428		Laz N = 213	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	421 (100)	316 (75.1)	425 (99.3)	183 (42.8)	213 (100)	97 (45.5)
Skin and subcutaneous tissue disorders						
Rash	260 (61.8)	65 (15.4)	131 (30.6)	3 (0.7)	95 (44.6)	4 (1.9)
Infections and infestations						
Paronychia	288 (68.4)	46 (10.9)	121 (28.3)	2 (0.5)	61 (28.6)	2 (0.9)
Gastrointestinal disorders						
Diarrhoea	123 (29.2)	9 (2.1)	190 (44.4)	3 (0.7)	68 (31.9)	4 (1.9)
General disorders and administration site conditions						
Oedema peripheral	150 (35.6)	8 (1.9)	24 (5.6)	0	24 (11.3)	0
Metabolism and nutrition disorders						
Hypoalbuminaemia	204 (48.5)	22 (5.2)	26 (6.1)	0	17 (8.0)	0
Injury, poisoning and procedural complications						
Infusion related reaction	265 (62.9)	27 (6.4)	0	0	0	0
Investigations						
ALT increased	152 (36.1)	21 (5.0)	57 (13.3)	8 (1.9)	50 (23.5)	6 (2.8)

Serious adverse events occurred in 205 of 421 subjects (48.7%) in the Ami/Laz group, 143 of 428 subjects (33.4%) in the Osi group, and 75 of 213 subjects (35.2%) in the Laz group. Those reported by ≥2% of subjects were pulmonary embolism (26 subjects [6.2%]); pneumonia (17 subjects [4.0%]); deep vein thrombosis (12 subjects [2.9%]); COVID-19 (10 subjects [2.4%]); and pleural effusion; and infusion related reaction (9 subjects each [2.1%]) in the Ami/Laz group, pneumonia (21 subjects [4.9%]); pleural effusion (17 subjects [4.0%]); dyspnoea (11 subjects [2.6%]); and pulmonary embolism; and COVID-19 (10 subjects each [2.3%]) in the Osi group, and pulmonary embolism (8 subjects [3.8%]); and pneumonia (7 subjects [3.3%]) in the Laz group. A causal relationship to study drug could not be ruled out for pulmonary embolism (17 subjects); infusion related reaction (9 subjects); deep vein thrombosis (4 subjects); pleural effusion (2 subjects); and pneumonia (1 subject) in the Ami/Laz group, pleural effusion (2 subjects); and pneumonia; and deep vein thrombosis (1 subject each) in the Osi group, and pulmonary embolism (2 subjects) in the Laz group.

Adverse events leading to study drug discontinuation occurred in 147 of 421 subjects (34.9%) in the Ami/Laz group, 58 of 428 subjects (13.6%) in the Osi group, and 28 of 213 subjects (13.1%) in the Laz group. Those reported by ≥2% of subjects in the Ami/Laz group were infusion related reaction (19 subjects [4.5%]);

paronychia (14 subjects [3.3%]); and rash (11 subjects [2.6%]), and there were no adverse events leading to study drug discontinuation reported by ≥2% of subjects in the Osi or Laz group. A causal relationship to study drug could not be ruled out for infusion related reaction (19 subjects); paronychia (13 subjects); and rash (11 subjects) in the Ami/Laz group.

7.3.4 Foreign phase I/II study (Study NSC2001) (Laz monotherapy)

7.3.4.1 Part A

Adverse events occurred in 3 of 3 subjects (100%) in the 20 mg cohort, 4 of 7 subjects (57.1%) in the 40 mg cohort, 6 of 6 subjects (100%) in the 80 mg cohort, 6 of 6 subjects (100%) in the 120 mg cohort, 5 of 6 subjects (83.3%) in the 160 mg cohort, 5 of 5 subjects (100%) in the 240 mg cohort, and 5 of 5 subjects (100%) in the 320 mg cohort. Those for which a causal relationship to study drug could not be ruled out occurred in 2 of 3 subjects (66.7%) in the 20 mg cohort, 2 of 7 subjects (28.6%) in the 40 mg cohort, 4 of 6 subjects (66.7%) in the 80 mg cohort, 5 of 6 subjects (83.3%) in the 120 mg cohort, 4 of 6 subjects (66.7%) in the 160 mg cohort, 5 of 5 subjects (100%) in the 240 mg cohort, and 4 of 5 subjects (80.0%) in the 320 mg cohort.

Adverse events reported by ≥30% of subjects were dyspepsia; headache; cough; and dyspnoea (2 subjects each [33.3%]) in the 80 mg cohort, nausea; and rash (3 subjects each [50.0%]); and vomiting; paraesthesia; paronychia; upper respiratory tract infection; cough; and arthralgia (2 subjects each [33.3%]) in the 120 mg cohort, pruritus (3 subjects [50.0%]); and dyspepsia; decreased appetite; rash; and nail disorder (2 subjects each [33.3%]) in the 160 mg cohort, diarrhoea (3 subjects [60.0%]); and abdominal pain upper; headache; paraesthesia; pruritus; dry eye; photophobia; and muscle spasms (2 subjects each [40.0%]) in the 240 mg cohort, and constipation; dyspepsia; decreased appetite; dizziness; pneumonia; and rash (2 subjects each [40.0%]) in the 320 mg cohort.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 20 mg cohort, 2 of 7 subjects (28.6%) in the 40 mg cohort, 2 of 6 subjects (33.3%) in the 80 mg cohort, 4 of 6 subjects (66.7%) in the 120 mg cohort, and 1 of 5 subjects (20.0%) in the 320 mg cohort. The reported serious adverse events were pneumonia (1 subject [33.3%]) in the 20 mg cohort, back pain; and gallbladder cancer (1 subject each [14.3%]) in the 40 mg cohort, dyspepsia; hypoaesthesia oral; and lumbar spinal stenosis (1 subject each [16.7%]) in the 80 mg cohort, pneumonia; gastroenteritis; pyrexia; and subdural haemorrhage (1 subject each [16.7%]) in the 120 mg cohort, and pneumonia (1 subject [20.0%]) in the 320 mg cohort. A causal relationship to study drug could not be ruled out for dyspepsia (1 subject) in the 80 mg cohort.

An adverse event leading to study drug discontinuation occurred in 1 of 7 subjects (14.3%) in the 40 mg cohort. The reported adverse event leading to study drug discontinuation was gallbladder cancer (1 subject), and its causal relationship to study drug was denied.

7.3.4.2 Part B

Adverse events occurred in 20 of 20 subjects (100%) in the 40 mg cohort, 12 of 14 subjects (85.7%) in the 80 mg cohort, 19 of 19 subjects (100%) in the 120 mg cohort, 16 of 17 subjects (94.1%) in the 160 mg cohort,

and 19 of 19 subjects (100%) in the 240 mg cohort. Those for which a causal relationship to study drug could not be ruled out occurred in 13 of 20 subjects (65.0%) in the 40 mg cohort, 9 of 14 subjects (64.3%) in the 80 mg cohort, 17 of 19 subjects (89.5%) in the 120 mg cohort, 14 of 17 subjects (82.4%) in the 160 mg cohort, and 17 of 19 subjects (89.5%) in the 240 mg cohort.

Adverse events reported by ≥30% of subjects were constipation (6 subjects [42.9%]) in the 80 mg cohort, pruritus (6 subjects [35.3%]) in the 160 mg cohort, and pruritus; and paraesthesia (9 subjects each [47.4%]); and muscle spasms; and decreased appetite (6 subjects each [31.6%]) in the 240 mg cohort.

Serious adverse events occurred in 6 of 20 subjects (30.0%) in the 40 mg cohort, 3 of 14 subjects (21.4%) in the 80 mg cohort, 4 of 19 subjects (21.1%) in the 120 mg cohort, 4 of 17 subjects (23.5%) in the 160 mg cohort, and 5 of 19 subjects (26.3%) in the 240 mg cohort. There were no serious adverse events reported by ≥2 subjects in any cohort.

Adverse events leading to study drug discontinuation occurred in 2 of 20 subjects (10.0%) in the 40 mg cohort, 1 of 14 subjects (7.1%) in the 80 mg cohort, and 1 of 19 subjects (5.3%) in the 240 mg cohort. The reported adverse events leading to study drug discontinuation were pneumonitis; and hepatocellular carcinoma (1 subject each [5.0%]) in the 40 mg cohort, nausea (1 subject [7.1%]) in the 80 mg cohort, and pneumonitis (1 subject [5.3%]) in the 240 mg cohort. A causal relationship to study drug could not be ruled out for pneumonitis (1 subject) in the 40 mg cohort, nausea (1 subject) in the 80 mg cohort, and pneumonitis (1 subject) in the 240 mg cohort.

7.3.4.3 Part C

Adverse events occurred in 43 of 43 subjects (100%) in the first-line cohort and 52 of 54 subjects (96.3%) in the second-line cohort. Those for which a causal relationship to study drug could not be ruled out occurred in 41 of 43 subjects (95.3%) in the first-line cohort and 47 of 54 subjects (87.0%) in the second-line cohort.

Adverse events reported by ≥30% of subjects were rash (23 subjects [53.5%]); pruritus; and diarrhoea (20 subjects each [46.5%]); paraesthesia (15 subjects [34.9%]); and decreased appetite (13 subjects [30.2%]) in the first-line cohort and rash (24 subjects [44.4%]) in the second-line cohort.

Serious adverse events occurred in 15 of 43 subjects (34.9%) in the first-line cohort and 14 of 54 subjects (25.9%) in the second-line cohort. Those reported by ≥2 subjects were pneumonia; and asthenia (3 subjects each [7.0%]); and sepsis; urinary tract infection; and pulmonary embolism (2 subjects each [4.7%]) in the first-line cohort and pneumonia (4 subjects [7.4%]); and pulmonary embolism (2 subjects [3.7%]) in the second-line cohort. A causal relationship to study drug could not be ruled out for pneumonia (1 subject) in the second-line cohort.

Adverse events leading to study drug discontinuation occurred in 7 of 43 subjects (16.3%) in the first-line cohort and 5 of 54 subjects (9.3%) in the second-line cohort. Those reported by ≥2 subjects were pulmonary embolism (2 subjects [4.7%]) in the first-line cohort, and their causal relationship to study drug was denied.

7.3.4.4 Part D

Adverse events occurred in all subjects in the 240 mg and 320 mg cohorts, and those for which a causal relationship to study drug could not be ruled out occurred in 15 of 15 subjects (100%) in the 240 mg cohort and 11 of 13 subjects (84.6%) in the 320 mg cohort.

Adverse events reported by ≥30% of subjects were diarrhoea (6 subjects [40.0%]); and nausea; dyspnoea; and anaemia (5 subjects each [33.3%]) in the 240 mg cohort and nausea (8 subjects [61.5%]); diarrhoea (7 subjects [53.8%]); and dyspnoea (4 subjects [30.8%]) in the 320 mg cohort.

Serious adverse events occurred in 7 of 15 subjects (46.7%) in the 240 mg cohort and 6 of 13 subjects (46.2%) in the 320 mg cohort. The reported serious adverse events were dyspnoea; and pain (2 subjects each [13.3%]); and pulmonary embolism; cerebrovascular accident; abdominal pain; nausea; vomiting; asthenia; pain in extremity; pathological fracture; and adrenalectomy (1 subject each [6.7%]) in the 240 mg cohort and bronchitis; COVID-19; upper respiratory tract infection; pulmonary embolism; palpitations; malignant neoplasm progression; and cognitive disorder (1 subject each [7.7%]) in the 320 mg cohort. A causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in 2 of 15 subjects (13.3%) in the 240 mg cohort and 1 of 13 subjects (7.7%) in the 320 mg cohort. The reported adverse events leading to study drug discontinuation were asthenia; and troponin I increased (1 subject each [6.7%]) in the 240 mg cohort and COVID-19 (1 subject [7.7%]) in the 320 mg cohort. A causal relationship to study drug was denied for all those events.

7.3.5 Foreign phase III study (Study 301)

Adverse events occurred in 189 of 196 subjects (96.4%) in the Laz group and 188 of 197 subjects (95.4%) in the gefitinib group, and those for which a causal relationship to study drug could not be ruled out occurred in 172 of 196 subjects (87.8%) in the Laz group and 168 of 197 subjects (85.3%) in the gefitinib group. Table 87 shows adverse events reported by ≥20% of subjects in either group.

Table 87. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Laz N = 196		Gefitinib N = 197	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	189 (96.4)	80 (40.8)	188 (95.4)	84 (42.6)
Skin and subcutaneous tissue disorders				
Rash	71 (36.2)	2 (1.0)	72 (36.5)	5 (2.5)
Pruritus	52 (26.5)	1 (0.5)	36 (18.3)	0
Nervous system disorders				
Paraesthesia	77 (39.3)	5 (2.6)	13 (6.6)	0
Gastrointestinal disorders				
Diarrhoea	51 (26.0)	5 (2.6)	77 (39.1)	1 (0.5)
Investigations				
ALT increased	30 (15.3)	2 (1.0)	59 (29.9)	18 (9.1)
AST increased	22 (11.2)	1 (0.5)	52 (26.4)	13 (6.6)

Serious adverse events occurred in 51 of 196 subjects (26.0%) in the Laz group and 51 of 197 subjects (25.9%) in the gefitinib group. Those reported by ≥2% of subjects were pulmonary embolism; and pneumonia (8 subjects each [4.1%]) in the Laz group and acute kidney injury (4 subjects [2.0%]) in the gefitinib group. A causal relationship to study drug could not be ruled out for pulmonary embolism (1 subject) in the Laz group and acute kidney injury (1 subject) in the gefitinib group.

Adverse events leading to study drug discontinuation occurred in 19 of 196 subjects (9.7%) in the Laz group, but not in the gefitinib group. There were no adverse events leading to study drug discontinuation reported by ≥2% of subjects.

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

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

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

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that Ami/Laz has efficacy in the treatment of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, and that Ami/Laz has acceptable safety

in view of its benefits. The drug product of Laz and its drug substance are both classified as powerful drugs. Ami/Laz is clinically meaningful because it offers a treatment option for patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC. PMDA considers that the use of prophylactic anticoagulation to prevent venous thromboembolism associated with Ami/Laz and other measures need to be further discussed.

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

Review Report (2)

February 14, 2025

Products Submitted for Approval

(1)

Brand Name	Rybrevant Intravenous Infusion 350 mg
Non-proprietary Name	Amivantamab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 2024[2)]

(2)

Brand Name	Lazcluze Tablets 80 mg, Lazcluze Tablets 240 mg
Non-proprietary Name	Lazertinib Mesilate Hydrate
Applicant	Janssen Pharmaceutical K.K.
Date of Application	April 8, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's conclusion:

On the basis of the considerations in Section "7.R.2 Efficacy" in the Review Report (1), the submitted data supported the efficacy of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy because a global phase III study in this patient population (MARIPOSA study) demonstrated the superiority of Ami/Laz to Osi and a clinically meaningful improvement in the primary endpoint of PFS as assessed by BICR.

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

1.2 Safety

PMDA's conclusion:

On the basis of the considerations in Section "7.R.3 Safety" in the Review Report (1), adverse events that require particular attention following administration of Ami/Laz in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC are shown in the table below. Although patients should be monitored for the adverse events listed in the table below during the use of Ami and Laz, Ami/Laz is tolerable as long as physicians with sufficient knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., patient monitoring, management of adverse events, and dose interruption of Ami or Laz.

Ami	In addition to infusion reactions, ILD, skin disorders (including paronychia), venous thromboembolism, fluid retention (including oedema and hypoalbuminemia), and diarrhoea (see "Review Report on Rybrevant Intravenous Infusion 350 mg as of August 14, 2024"), arterial thromboembolism (Ami in combination with Laz)
Laz	ILD, venous thromboembolism, arterial thromboembolism (Laz in combination with Ami), hepatic dysfunction, severe diarrhoea, skin disorders (including paronychia), cardiac failure, and corneal disorders

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

- Given the incidence of adverse events in the MARIPOSA study, whether to use Ami/Laz should be decided carefully according to the patient's condition, and prompt and appropriate measures should be taken in the event of adverse events associated with Ami/Laz. Thus, the reference information to decide whether to use Ami/Laz (e.g., the incidence of adverse events in the MARIPOSA study, the information obtained from elderly patients enrolled in the MARIPOSA study, the patient population for whom Ami/Laz is recommended based on the MARIPOSA study) and the reference information in the event of adverse events associated with Ami/Laz (e.g., management of adverse events in the MARIPOSA study) should be provided appropriately to healthcare professionals in clinical practice.

Based on the above, taking account of the above comment from the expert advisors, PMDA instructed the applicant to appropriately provide the reference information for treatment with Ami/Laz to healthcare professionals in clinical practice. The applicant agreed to do so.

1.3 Clinical positioning and indications

PMDA's conclusion:

On the basis of the considerations in Section "7.R.4 Clinical positioning and indications" in the Review Report (1), the statements in the table below should be included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for Ami and Laz. The PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS sections of the package inserts for Ami and Laz should advise that whether to use Ami/Laz in patients aged ≥65 years should be decided carefully according to individual patients' conditions, and should provide the information on the incidence of adverse events by age group in the MARIPOSA study.

	Indications	Precautions Concerning Indications
Ami*	● *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC ● *EGFR* mutation-positive unresectable advanced or recurrent NSCLC	[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation and other characteristics of patients enrolled in the clinical study and of the efficacy and safety of Ami. ● Ami should be used in patients with an *EGFR* exon 20 insertion mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing. [*EGFR* mutation-positive unresectable advanced or recurrent NSCLC] ● The efficacy and safety of Ami in the neoadjuvant or adjuvant setting have not been established. ● Ami should be used in patients with an *EGFR* mutation (excluding *EGFR* exon 20 insertion mutations) as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
Laz	*EGFR* mutation-positive unresectable advanced or recurrent NSCLC	● The efficacy and safety of Laz in the neoadjuvant or adjuvant setting have not been established. ● Laz should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.

* Underline denotes additions to the approved labeling.

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

Based on the above, PMDA instructed the applicant to include the above statements in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections, and the applicant agreed to do so. PMDA also instructed the applicant to include a precautionary statement regarding the use of Ami/Laz in patients aged ≥65 years in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS sections of the package inserts for Ami and Laz. The applicant agreed to do so and responded as follows.

Table 88 and Figure 12 show the results of the final analysis of OS (data cutoff date of December 4, 2024) and the Kaplan-Meier curves, respectively, in the MARIPOSA study, which have become available after the Review Report (1) was finalized. Table 89 and Table 90 show the results of the final analysis of OS (data cutoff date of December 4, 2024) and the final analysis of PFS (data cutoff date of August 11, 2023) for age subgroups (cutoff values, 65 years, 70 years, and 75 years), respectively. Although the hazard ratios of OS and PFS in patients aged ≥65 years were above 1, the results in the subgroups of older patients, i.e., patients aged ≥70 years and patients aged ≥75 years, showed a similar trend to the results of the overall population. Given these findings, the above results of the subgroup analyses do not deny the efficacy of Ami/Laz in elderly patients.

Table 88. Results of final analysis of OS (FAS, data cutoff date of December 4, 2024)

	Ami/Laz	Osi
N	429	429
No. of events (%)	173 (40.3)	217 (50.6)
Median [95% CI] (months)	－ [42.94, －]	36.73 [33.41, 41.03]
Hazard ratio [95% CI]*1, 2	0.75 [0.61, 0.92]	
P-value (two-sided)*3	0.0048	

－, Not estimable

*1 A Cox proportional-hazards model stratified by *EGFR* mutation type (Ex19del, L858R), race (Asian, non-Asian), and history of brain metastasis (yes, no)

*2 The 95.16% CI corresponding to the significance level was [0.61, 0.92].

*3 Stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model), a significance level (two-sided) of 0.0484

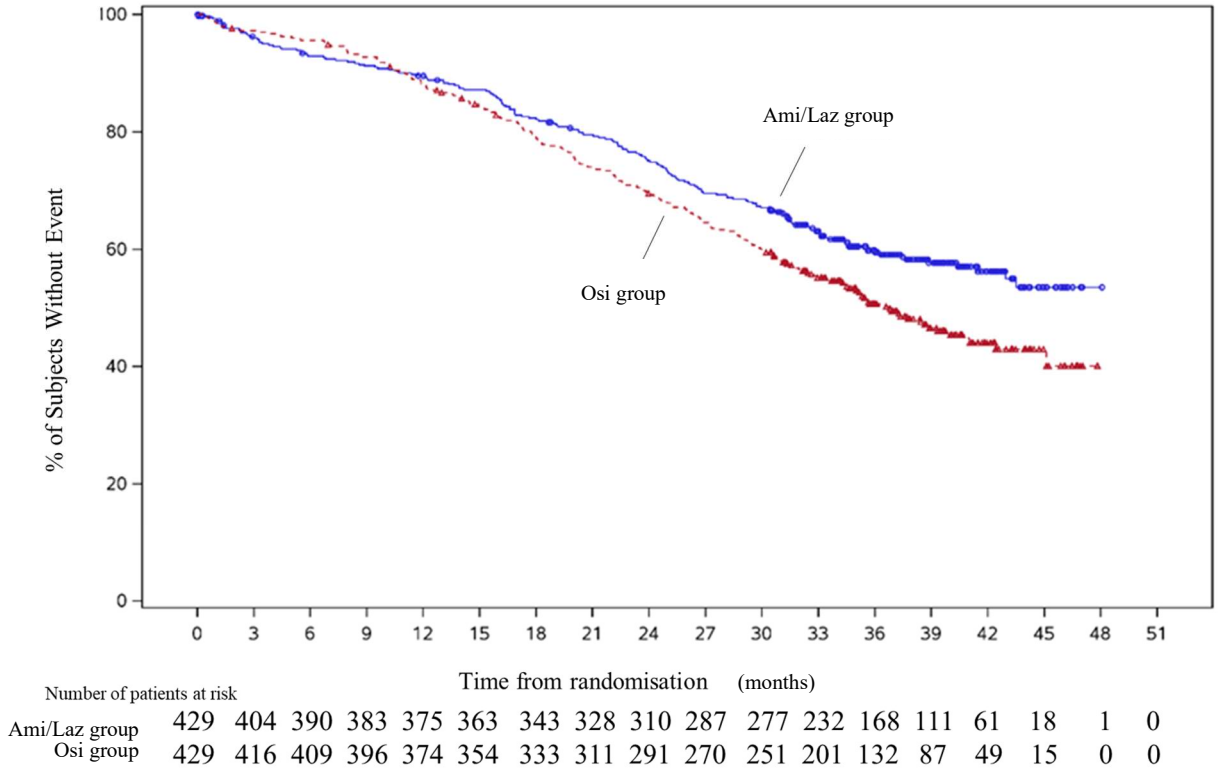

Figure 12. Kaplan-Meier curves of OS at the time of final analysis (FAS, data cutoff date of December 4, 2024)

Table 89. Results of final analysis of OS by age group (FAS, data cutoff date of December 4, 2024)

Age group	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
<65 years	Ami/Laz	235	76 (32.3)	－ [－, －]	0.53 [0.40, 0.70]
	Osi	237	123 (51.9)	35.61 [31.05, 42.41]	
≥65 years	Ami/Laz	194	97 (50.0)	35.61 [30.42, －]	1.11 [0.84, 1.48]
	Osi	192	94 (49.0)	37.72 [34.23, －]	
<70 years	Ami/Laz	320	125 (39.1)	－ [42.94, －]	0.72 [0.57, 0.91]
	Osi	310	156 (50.3)	36.73 [32.43, 45.11]	
≥70 years	Ami/Laz	109	48 (44.0)	43.50 [31.21, －]	0.86 [0.59, 1.26]
	Osi	119	61 (51.3)	37.32 [29.77, －]	
<75 years	Ami/Laz	378	147 (38.9)	－ [42.94, －]	0.75 [0.60, 0.93]
	Osi	376	185 (49.2)	37.22 [34.37, 45.11]	
≥75 years	Ami/Laz	51	26 (51.0)	37.59 [23.85, －]	0.79 [0.47, 1.33]
	Osi	53	32 (60.4)	32.76 [23.36, 39.79]	

－, Not estimable, * Unstratified Cox proportional hazards model

Table 90. Results of final analysis of PFS by age group (BICR, FAS, data cutoff date of August 11, 2023)

Age group	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio* [95% CI]
<65 years	Ami/Laz	235	94 (40.0)	－ [20.47, －]	0.50 [0.39, 0.65]
	Osi	237	153 (64.6)	14.75 [12.91, 16.59]	
≥65 years	Ami/Laz	194	98 (50.5)	19.12 [16.07, 24.05]	1.06 [0.80, 1.41]
	Osi	192	99 (51.6)	20.14 [16.59, 23.92]	
<70 years	Ami/Laz	320	142 (44.4)	23.98 [18.53, －]	0.67 [0.54, 0.83]
	Osi	310	186 (60.0)	15.87 [13.57, 18.43]	
≥70 years	Ami/Laz	109	50 (45.9)	20.30 [16.62, －]	0.83 [0.58, 1.20]
	Osi	119	66 (55.5)	18.66 [16.36, 23.59]	
<75 years	Ami/Laz	378	165 (43.7)	24.05 [18.66, －]	0.70 [0.57, 0.85]
	Osi	376	220 (58.5)	16.62 [14.78, 18.50]	
≥75 years	Ami/Laz	51	27 (52.9)	20.30 [16.46, －]	0.77 [0.46, 1.30]
	Osi	53	32 (60.4)	15.90 [11.17, 20.40]	

－, Not estimable, *Unstratified Cox proportional hazards model

PMDA accepted the applicant's explanation.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the statements in the table below should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for Ami and Laz.

<table>
<tr><th></th><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>Ami*</td><td>
[EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC]
The usual adult dosage of amivantamab (Ami) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.
<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="5">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,400 mg</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>1,750 mg</td></tr>
<tr><td rowspan="5">Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,400 mg</td></tr>
<tr><td>Day 8, Day 15</td><td>1,750 mg</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,750 mg</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>2,100 mg</td></tr>
</table>
[EGFR mutation-positive unresectable advanced or recurrent NSCLC]
The usual adult dosage of amivantamab (Ami) in combination with Laz is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.
<table>
<tr><th>Body weight</th><th>Cycle</th><th>Dosing schedule</th><th>Dose</th></tr>
<tr><td rowspan="4">Less than 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>700 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,050 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td></tr>
<tr><td rowspan="4">Greater than or equal to 80 kg</td><td rowspan="3">Cycle 1</td><td>Day 1</td><td>350 mg</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td></tr>
<tr><td>Day 8, Day 15, Day 22</td><td>1,400 mg</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td></tr>
</table>
</td><td>
● Administer the diluted solution according to the infusion rates in the table below.
Doses and infusion rates of Ami (Ami in combination with carboplatin and pemetrexed sodium)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>33 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>1,750 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,400 mg</td><td>25 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,750 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,750 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 2</td><td>Day 1</td><td>1,750 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 3 onwards</td><td>Day 1</td><td>2,100 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.
Doses and infusion rates of Ami (Ami in combination with Laz)
<table>
<tr><th rowspan="2">Cycle</th><th rowspan="2">Dosing schedule</th><th rowspan="2">Dose (/250 mL)</th><th colspan="2">Infusion rate</th></tr>
<tr><th>Initial infusion rate</th><th>Subsequent infusion rate^{Note)}</th></tr>
<tr><td colspan="5">Body weight less than 80 kg</td></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 8</td><td>1,050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 15, Day 22</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td colspan="5">Body weight greater than or equal to 80 kg</td></tr>
<tr><td rowspan="5">Cycle 1</td><td>Day 1</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Day 2</td><td>1,050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>Day 8</td><td>1,400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>Day 15</td><td>1,400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Day 22</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>Cycle 2 onwards</td><td>Day 1, Day 15</td><td>1,400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.
● Prior to the initial infusion of Ami (Cycle 1, Day 1 and Day 2), glucocorticoids, antihistamines, and antipyretics should be administered, and H_2 receptor antagonists and antiemetics should also be administered as needed to reduce the risk of infusion reactions. For subsequent infusions from Cycle 1 Day 8 onwards, antihistamines and antipyretics should be administered, and glucocorticoids, H_2 receptor antagonists, and antiemetics should also be administered as needed.
● When administering Ami in combination with Laz, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.
● Recommended Ami dosage modifications for adverse reactions [see Section "7.R.5.3 Recommended dosage modifications" in the Review Report (1)]
</td></tr>
<tr><td>Laz</td><td>The usual adult dosage is 240 mg of Laz orally once daily administered in combination with Ami. The dosage should be reduced, as appropriate, according to the patient's condition.</td><td>● When administering Laz in combination with Ami, administer oral apixaban 2.5 mg BID to prevent venous thromboembolism for the first 4 months of treatment.
● Recommended Laz dosage modifications for adverse reactions [see Section "7.R.5.3 Recommended dosage modifications" in the Review Report (1)]</td></tr>
</table>

* Underline denotes additions to the approved labeling.

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

Based on the above, PMDA instructed the applicant to include the above statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections, and the applicant agreed to do so.

1.5 RMP (draft) and post-marketing investigations

On the basis of the considerations in Section "7.R.6 RMP (draft)" in the Review Report (1), PMDA has concluded that the RMPs (draft) for Ami and Laz should include the safety specifications presented in Table 91 and Table 92, respectively.

Table 91. Safety and efficacy specifications in the RMP (draft) for Ami

Safety specification		
Important identified risks	Important potential risks	Important missing information
● Infusion reactions ● ILD ● Severe skin disorders ● Venous thromboembolism (Ami in combination with Laz)	● Venous thromboembolism (excluding Ami in combination with Laz) ● Arterial thromboembolism (Ami in combination with Laz) ● Fluid retention ● Severe diarrhoea ● Embryo-fetal toxicity	None
Efficacy specification		
None		

Underline denotes additions in the present partial change application.

Table 92. Safety and efficacy specifications in the RMP (draft) for Laz

Safety specification		
Important identified risks	Important potential risks	Important missing information
● ILD ● Venous thromboembolism (Laz in combination with Ami) ● Hepatic dysfunction ● Severe diarrhoea ● Severe skin disorders ● Cardiac failure	● Venous thromboembolism (excluding Laz in combination with Ami) ● Arterial thromboembolism (Laz in combination with Ami) ● Corneal disorders ● Use in patients with severe hepatic impairment ● Embryo-fetal toxicity	None
Efficacy specification		
None		

PMDA's conclusion:

On the basis of the considerations in Section "7.R.7 Post-marketing investigations" in the Review Report (1), there is no need to conduct post-marketing surveillance in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC, immediately after obtaining approval, and the applicant may ensure the implementation of the following measures through early post-marketing phase vigilance and routine pharmacovigilance practices: provide information on adverse events that require particular attention following administration of Ami/Laz [see Section "7.R.3 Safety" in the Review Report (1)] to healthcare professionals in clinical practice; collect safety information regarding treatment with Ami/Laz; and take appropriate safety measures based on the currently available information and future information.

At the Expert Discussion, the expert advisors supported the above conclusions by PMDA.

In view of the discussion above, PMDA has concluded that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 93 and Table 94 under the RMPs (draft) for Ami and Laz, respectively.

Table 93. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the RMP (draft) for Ami

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
● Early post-marketing phase vigilance (*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC) ● Early post-marketing phase vigilance (*EGFR* mutation (excluding *EGFR* exon 20 insertion mutations)-positive unresectable advanced or recurrent NSCLC) ● Post-marketing database survey (venous thromboembolism)	None	● Disseminate data gathered during early post-marketing phase vigilance (*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent NSCLC) ● Disseminate data gathered during early post-marketing phase vigilance (*EGFR* mutation (excluding *EGFR* exon 20 insertion mutations)-positive unresectable advanced or recurrent NSCLC) ● Develop and distribute information materials to healthcare professionals ● Develop and distribute information materials to patients

Underline denotes planned activities for the additional indication in the present application.

Table 94. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the RMP (draft) for Laz

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
● Early post-marketing phase vigilance	None	● Disseminate data gathered during early post-marketing phase vigilance ● Develop and distribute information materials to healthcare professionals ● Develop and distribute information materials to patients

1.6 Others

1.6.1 Companion diagnostic as an aid in identifying patients eligible for treatment with Ami/Laz

The applicant's explanation:

Roche Diagnostics K.K. submitted a partial change application for a companion diagnostic, "the cobas EGFR Mutation Test v2.0," as an aid in identifying patients eligible for treatment with Ami/Laz. The concordance analysis was performed with tumor tissue samples, and good agreement in the detection between "the Cobas EGFR Mutation Test v2.0" and the local tests used in the MARIPOSA study was demonstrated. Based on this finding etc., after the approval of this partial change application, "the cobas EGFR Mutation Test v2.0" should be used for selection of eligible patients for treatment with Ami/Laz.

PMDA accepted the applicant's explanation.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that each product may be approved for the indication and dosage and administration shown below, with the following condition, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated in the post-marketing setting, and provided that the proper use of Ami and Laz is ensured under the supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. The re-examination period for the present application for Ami is the remainder of the re-examination period for the initial approval of Ami (until September 23, 2032). Since Laz is a drug with a new active ingredient, the re-examination period is 8 years.

(Rybrevant Intravenous Infusion 350 mg)

Indications (Underline denotes additions.)

EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer

EGFR mutation-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration (Underline denotes additions.)

[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

The usual adult dosage of amivantamab (genetical recombination) in combination with carboplatin and pemetrexed sodium is provided in the table below. It is administered by intravenous infusion in 3-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15	1,400 mg
	Cycle 2	Day 1	1,400 mg
	Cycle 3 onwards	Day 1	1,750 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,400 mg
		Day 8, Day 15	1,750 mg
	Cycle 2	Day 1	1,750 mg
	Cycle 3 onwards	Day 1	2,100 mg

[*EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

The usual adult dosage of amivantamab (genetical recombination) in combination with lazertinib mesilate is provided in the table below. It is administered by intravenous infusion in 4-week cycles. The dosage should be reduced, as appropriate, according to the patient's condition.

Body weight	Cycle	Dosing schedule	Dose
Less than 80 kg	Cycle 1	Day 1	350 mg
		Day 2	700 mg
		Day 8, Day 15, Day 22	1,050 mg
	Cycle 2 onwards	Day 1, Day 15	1,050 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1,050 mg
		Day 8, Day 15, Day 22	1,400 mg
	Cycle 2 onwards	Day 1, Day 15	1,400 mg

Approval Condition

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

Warnings (Underline denotes additions.)

1. Rybrevant should be administered only to patients eligible for Rybrevant therapy, under the supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

2. As cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored, e.g., detection of initial symptoms (dyspnoea, cough, pyrexia, etc.) and regular thoracic imaging. If abnormalities are observed, Rybrevant should be discontinued, and the administration of corticosteroids or any other appropriate measures should be taken. Patients should be closely monitored for serious adverse reactions such as interstitial lung disease in an inpatient setting or with professional supervision especially during early treatment.
3. Prior to initiation of treatment, a chest CT scan should be performed, and a medical history should be taken to confirm the presence or absence of current or prior interstitial lung disease and then carefully decide whether to use Rybrevant.
4. In patients receiving Rybrevant in combination with lazertinib, venous thromboembolism, including deep vein thrombosis and pulmonary embolism, including fatal events, have been reported. Carefully decide whether to use Rybrevant after confirming the presence or absence of a history of venous thromboembolism, etc. Patients should be closely monitored during treatment with Rybrevant for signs or symptoms suspected of venous thromboembolism, including leg pain/swelling, sudden dyspnoea, shortness of breath, and chest pain.

Contraindication (No change)

Patients with a history of hypersensitivity to any of the ingredients of Rybrevant

Precautions Concerning Indications (Underline denotes additions.)

[*EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

1. Rybrevant should be used in patients with an *EGFR* exon 20 insertion mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
2. Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the type of genetic mutation and other characteristics of patients enrolled in the clinical study and of the efficacy and safety of Rybrevant.
3. The efficacy and safety of Rybrevant in the neoadjuvant or adjuvant setting have not been established.

[*EGFR* mutation-positive unresectable advanced or recurrent non-small cell lung cancer]

4. Rybrevant should be used in patients with an *EGFR* mutation (excluding *EGFR* exon 20 insertion mutations) as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
5. The efficacy and safety of Rybrevant in the neoadjuvant or adjuvant setting have not been established.

Precautions Concerning Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions.)

1. Prior to the initial infusion of Rybrevant (Cycle 1, Day 1 and Day 2), glucocorticoids, antihistamines, and antipyretics should be administered, and H_2 receptor antagonists and antiemetics should also be administered as needed to reduce the risk of infusion reactions. For subsequent infusions from Cycle 1

Day 8 onwards, antihistamines and antipyretics should be administered, and glucocorticoids, H_2 receptor antagonists, and antiemetics should also be administered as needed.

2. Administer the diluted solution according to the infusion rates in the table below.

Doses and infusion rates of Rybrevant (Rybrevant in combination with carboplatin and pemetrexed sodium)

Cycle	Dosing schedule	Dose (/250 mL)	Infusion rate	
			Initial infusion rate	Subsequent infusion rate[Note)]
Body weight less than 80 kg				
Cycle 1	Day 1	350 mg	50 mL/h	75 mL/h
	Day 2	1,050 mg	33 mL/h	50 mL/h
	Day 8	1,400 mg	65 mL/h	
	Day 15	1,400 mg	85 mL/h	
Cycle 2	Day 1	1,400 mg	125 mL/h	
Cycle 3 onwards	Day 1	1,750 mg	125 mL/h	
Body weight greater than or equal to 80 kg				
Cycle 1	Day 1	350 mg	50 mL/h	75 mL/h
	Day 2	1,400 mg	25 mL/h	50 mL/h
	Day 8	1,750 mg	65 mL/h	
	Day 15	1,750 mg	85 mL/h	
Cycle 2	Day 1	1,750 mg	125 mL/h	
Cycle 3 onwards	Day 1	2,100 mg	125 mL/h	

Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

Doses and infusion rates of Rybrevant (Rybrevant in combination with lazertinib)

Cycle	Dosing schedule	Dose (/250 mL)	Infusion rate	
			Initial infusion rate	Subsequent infusion rate[Note)]
Body weight less than 80 kg				
Cycle 1	Day 1	350 mg	50 mL/h	75 mL/h
	Day 2	700 mg	50 mL/h	75 mL/h
	Day 8	1,050 mg	85 mL/h	
	Day 15, Day 22	1,050 mg	125 mL/h	
Cycle 2 onwards	Day 1, Day 15	1,050 mg	125 mL/h	
Body weight greater than or equal to 80 kg				
Cycle 1	Day 1	350 mg	50 mL/h	75 mL/h
	Day 2	1,050 mg	35 mL/h	50 mL/h
	Day 8	1,400 mg	65 mL/h	
	Day 15	1,400 mg	85 mL/h	
	Day 22	1,400 mg	125 mL/h	
Cycle 2 onwards	Day 1, Day 15	1,400 mg	125 mL/h	

Note) In the absence of infusion reactions, the initial infusion rate may be increased to the subsequent infusion rate after 2 hours.

3. When administering Rybrevant in combination with lazertinib, administer apixaban 2.5 mg orally twice daily to prevent venous thromboembolism for the first 4 months of combination treatment.

~~3~~4. In the event of adverse reactions to Rybrevant, reduce the dose, interrupt, withhold, or discontinue Rybrevant, as per the tables below.

Rybrevant dose reductions for adverse reactions

Dose at which the adverse reaction occurred	First dose reduction	Second dose reduction	Third dose reduction
1,050 mg	700 mg	350 mg	Discontinue Rybrevant
1,400 mg	1,050 mg	700 mg	
1,750 mg	1,400 mg	1,050 mg	
2,100 mg	1,750 mg	1,400 mg	

Recommended Rybrevant dosage modifications for adverse reactions

Infusion Reactions

Severity*	Dosage Modifications
Grade 1 or 2	● Interrupt Rybrevant infusion. ● Upon resolution of symptoms, resume the infusion at 50% of the infusion rate at which the reaction occurred. ● If there are no additional symptoms after 30 minutes, the infusion rate may be increased to 100% of the infusion rate at the time of interruption. In the absence of additional symptoms, the rate may be increased per the recommended infusion rate after 2 hours. ● In the case of second interruption for Grade 2 infusion reaction, consider discontinuation of further treatment on the same day.
Grade 3	● Discontinue further treatment on the same day. ● Decide whether to continue with subsequent dosing according to the patient's condition. Decide the infusion rate according to the patient's condition, based on the guidance for Grade 2 infusion reactions. ● For recurrent Grade 3 infusion reactions, permanently discontinue Rybrevant.
Grade 4	Permanently discontinue Rybrevant.

Interstitial lung disease

Diagnosis	Dosage Modifications
Suspected	Withhold Rybrevant.
Confirmed	Permanently discontinue Rybrevant.

Venous thromboembolism (Rybrevant in combination with lazertinib)

Situation	Dosage modifications
Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withold Rybrevant until the patient is clinically stable.
Recurrent venous thromboembolism despite therapeutic level anticoagulation	Permanently discontinue Rybrevant.

Skin or nail reactions

Severity*	Dosage Modifications
Grade 1 ~~or 2~~	If there is no improvement after 2 weeks, consider dose reduction.
Grade 2	● When Rybrevant is used in combination with lazertinib, consider dose reduction. ● If there is no improvement after 2 weeks, consider dose reduction.
Grade 3	● Withhold Rybrevant until recovery to Grade ≤2~~,~~, and resume Rybrevant at a reduced dose. ● When Rybrevant is used in combination with lazertinib, withhold Rybrevant and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction and then resume Rybrevant. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Rybrevant.
Grade 4	Permanently discontinue Rybrevant.
Severe bullous, blistering or exfoliating skin conditions	

Other adverse reactions

Severity*	Dosage Modifications
Grade 2	● Consider dose interruption. ● Consider resuming at a reduced dose if there is improvement ~~recovery occurs~~ after 1 week. ● When Rybrevant is used in combination with lazertinib, consider dose interruption or dose reduction. Consider resuming at the same dose or at a reduced dose if there is improvement within 28 days. Consider resuming at a reduced dose if there is improvement after 28 days.
Grade 3	● Withhold Rybrevant until recovery to Grade ≤1 or baseline. ● Resume at the same dose if recovery occurs within 1 week. ● Resume at a reduced dose if recovery occurs after 1 week but within 4 weeks. ● Consider permanent discontinuation of Rybrevant if recovery does not occur within 4 weeks.
Grade 4	Permanently discontinue as a rule.

* Severity grade based on NCI-CTCAE v5.0~~4.03~~

(Lazcluze Tablets 80 mg, Lazcluze Tablets 240 mg)

Indication

EGFR mutation-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 240 mg of lazertinib orally once daily administered in combination with amivantamab (genetical recombination). The dosage should be reduced, as appropriate, according to the patient's condition.

Approval Condition

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

Warnings

1. Lazcluze should be administered only to patients eligible for Lazcluze therapy, under the supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.
2. As cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored, e.g., detection of initial symptoms (dyspnoea, cough, pyrexia, etc.) and regular thoracic imaging. If abnormalities are observed, Lazcluze should be discontinued, and the administration of corticosteroids or any other appropriate measures should be taken. Patients should be closely monitored for serious adverse reactions such as interstitial lung disease in an inpatient setting or with professional supervision especially during early treatment.
3. Prior to initiation of treatment, a chest CT scan should be performed, and a medical history should be taken to confirm the presence or absence of current or prior interstitial lung disease and then carefully decide whether to use Lazcluze.
4. In patients receiving Lazcluze in combination with Amivantamab (genetical recombination), venous thromboembolism, including deep vein thrombosis and pulmonary embolism, including fatal events, have been reported. Carefully decide whether to use Lazcluze after confirming the presence or absence of a history of venous thromboembolism, etc. Patients should be closely monitored during treatment with Lazcluze for signs or symptoms suspected of venous thromboembolism, including leg pain/oedema, sudden dyspnoea, shortness of breath, and chest pain.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients of Lazcluze

Precautions Concerning Indication

1. Lazcluze should be used in patients with an *EGFR* mutation as detected by testing performed by a pathologist or laboratory with sufficient experience. The approved *in vitro* diagnostic or medical device should be used for testing.
2. The efficacy and safety of Lazcluze in the neoadjuvant or adjuvant setting have not been established.

Precautions Concerning Dosage and Administration

1. When administering Lazcluze in combination with amivantamab (genetical recombination), administer apixaban 2.5 mg orally twice daily to prevent venous thromboembolism for the first 4 months of treatment.
2. In the event of adverse reactions to Lazcluze, reduce the dose, withhold or discontinue Lazcluze, as per the tables below.

Lazcluze dose reductions for adverse reactions

Dose reduction	First dose reduction	Second dose reduction		Third dose reduction
Dose	160 mg/day	80 mg/day		Discontinue Lazcluze

Recommended dosage modifications for adverse reactions

Interstitial lung disease

Diagnosis	Dosage Modifications
Suspected	Withhold Lazcluze.
Confirmed	Permanently discontinue Lazcluze.

Venous thromboembolism (Lazcluze in combination with amivantamab (genetical recombination))

Situation	Dosage Modifications
Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withold Lazcluze until the patient is clinically stable.
Recurrent venous thromboembolism despite therapeutic anticoagulation	Permanently discontinue Lazcluze. Treatment can continue with Lazcluze at the same dose level at the discretion of the physician.

Skin or nail reactions

Severity[Note1)]	Dosage Modifications
Grade 2	● Consider dose reduction.[Note2)] ● Monitor the patient after 2 weeks.
Grade 3	Withhold Lazcluze and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction[Note2)] and then resume Lazcluze. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Lazcluze.
Grade 4	Withhold Lazcluze and monitor the patient once weekly. If recovery to Grade ≤2 occurs within 2 weeks, consider dose reduction and then resume Lazcluze. If recovery to Grade ≤2 does not occur within 2 weeks, permanently discontinue Lazcluze.
Severe bullous, blistering or exfoliating skin conditions	Permanently discontinue Lazcluze.

Other adverse reactions

Severity[Note 1)]	Dosage Modifications
Grade 2	● Consider dose interruption or dose reduction. ● Consider resuming at the same dose or at a reduced dose if there is improvement within 28 days. Consider resuming at a reduced dose if there is improvement after 28 days.
Grade 3	● Withhold Lazcluze until recovery to Grade ≤1 or baseline. ● Consider resuming[Note3)] at a reduced dose if recovery occurs within 4 weeks. Consider permanent discontinuation of Lazcluze if recovery does not occur within 4 weeks.
Grade 4	● Permanently discontinue as a rule. ● If Lazcluze is not permanently discontinued, withhold Lazcluze until recovery to Grade ≤1 or baseline. Resume[Note3)] at a reduced dose if recovery occurs within 4 weeks. Permanently discontinue Lazcluze if recovery does not occur within 4 weeks.

Note 1) Severity grade based on NCI-CTCAE v5.0
Note 2) Preferentially reduce the dose of amivantamab (genetical recombination) first unless the adverse reaction is strongly suspected to be related to Lazcluze.
Note 3) Resume Lazcluze and then resume amivantamab (genetical recombination) at a reduced dose unless the adverse reaction is strongly suspected to be related to Lazcluze.

List of Abbreviations

ADCC	antibody dependent cellular cytotoxicity
afatinib	afatinib maleate
A/G ratio	Albumin/Globulin ratio
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Ami	amivantamab (genetical recombination)
Ami/Laz	Ami in combination with Laz
application	marketing application
ASBT	apical sodium-dependent bile acid transporter
ASCO guideline	Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Guideline Update
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under concentration-time curve
AUC_{24h}	AUC from time zero to 24 hours
$AUC_{24h, ss}$	AUC from time zero to 24 hours at steady state
AUC_{120h}	AUC from time zero to 120 hours
AUC_{168h}	AUC from time zero to 168 hours
AUC_{inf}	AUC from time zero to infinity
AUC_{last}	AUC from time zero to the last measurable time
AUC_{tau}	AUC over the dosing interval
BA	bioavailability
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	bis in die
BSEP	bile salt export pump
C_{avg}	average concentration
C_{eoi}	serum concentration at the end of infusion
C_{max}	maximum concentration
$C_{max, ss}$	maximum concentration at steady state
C_{trough}	trough concentration
CI	confidence interval
CL_{int}	intrinsic clearance
CL/F	apparent total body clearance
COVID-19	coronavirus disease
CPP	critical process parameter
CQA	critical quality attribute
CrCL	creatinine clearance
CYP	cytochrome P450
^{14}C-Laz	^{14}C-labeled Laz
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGFR-TKI	epidermal growth factor receptor-tyrosine kinase inhibitor

ERK	extracellular signal-regulated kinase
erlotinib	erlotinib hydrochloride
ESMO guidelines	Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
EU	European Union
Ex19del	*EGFR* exon 19 deletions
FAS	full analysis set
FRET	fluorescence resonance energy transfer
GALT	Gut-associated lymphoid tissue
GC	gas chromatography
GGT	γ-glutamyl transferase
GHS	Globally Harmonized System
GI_{50}	half-maximal growth inhibitory concentration
GST	glutathione *S*-transferase
HER	human epidermal growth factor receptor
hERG	human *ether-a-go-go* related gene
HGF	hepatocyte growth factor
HTRF	homogeneous time-resolved fluorescence
ICH Q1E guideline	Guideline on Evaluation of Stability Data (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guideline	Revision of the Guideline on Impurities in New Drug Substances (PMSB/ELD Notification No.1216001 dated December 16, 2002)
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
Japanese clinical practice guideline	Clinical Practice Guideline for Lung Cancer, the Japan Lung Cancer Society ed.
K_I	concentration causing half-maximal inactivation
k_{inact}	maximum inactivation rate constant
Laz	lazertinib mesilate hydrate
LC	liquid chromatography
LC-MS/MS	liquid chromatography-tandem mass spectrometry
L858R	A mutation of leucine (L) at position 858 of EGFR substituted with arginine (R)
MARIPOSA study	Study 73841937NSC3003
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor
metformin	metformin hydrochloride
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MS	mass spectrometry
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines (Cancer-Associated Venous Thromboembolic Disease)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cancer-Associated Venous Thromboembolic Disease
NCCN guidelines (NSCLC)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer

NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query
NIR	near infrared spectroscopy
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance spectroscopy
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
Osi	osimertinib mesylate
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PALOMA-3 study	Study 61186372NSC3004
PAPILLON study	Study 61186372NSC3001
PAR	proven acceptable range
partial change application	application for partial change of marketing approval
PBPK	physiologically based pharmacokinetics
PEM	pemetrexed sodium hydrate
PFS	progression free survival
P-gp	P-glycoprotein
PIF	photo irritation factor
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
PTP	press through packaging
QD	quaque die
QT	QT interval
QTc	QT interval corrected
QTcP	Population-specific heart rate correction for QT
ΔQTcP	change from baseline in QTcP
QW	quaque 1 week
Q2W	quaque 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rosuvastatin	rosuvastatin calcium
RP2D	recommended Phase II dose
RTD	residence time distribution
RTRT	real time release testing
SI	stimulation index
SMQ	standardized MedDRA queries
SOC	system organ class
Study 101	Study YH25448-101
Study 301	Study YH25448-301
Study EDI1001	Study 61186372EDI1001
Study NSC1001	Study 73841937NSC1001
Study NSC1002	Study73841937NSC1002
Study NSC1003	Study 73841937NSC1003
Study NSC1004	Study 73841937NSC1004
Study NSC1006	Study 73841937NSC1006
Study NSC1007	Study 73841937NSC1007
Study NSC1008	Study 73841937NSC1008

Study NSC1009	Study 73841937NSC1009
Study NSC2001	Study YH25448-201
$t_{1/2}$	elimination half-life
T790M	A mutation of threonine (T) at position 790 of EGFR substituted with methionine (M)
t_{max}	time to reach maximum concentration
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
UV	ultraviolet spectroscopy
V_2/F	apparent central compartment volume of distribution
V_{ss}	volume of distribution at steady state